SULPHUR-CONTAINING AMINO ACIDS METABOLISM IN EXPERIMENTAL HYPER- AND HYPOTHYROIDISM IN RATS

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Hyper- and hypothyroidism are the most common endocrine disorders, leading to metabolic disorders that increase the risk of cardiovascular diseases [1]. Recent studies have shown insulin resistance in patients with hypothyroidism, which, in its turn, leads to endothelium lesions and development of atherosclerosis and significantly increases the risk of coronary heart disease [2,3]. It is established that hyperhomocysteinemia (HHCy) is an independent risk factor of atherosclerosis [4]. HHCy contributes to the development of endothelial dysfunction and oxidative stress, inhibits proliferation of smooth muscles cells and enhances platelet aggregation [5,6].

The research [3] proved that in hypothyroidism HHCy is associated with hypercholesterolemia and this combination may be an important risk factor for development of cardiovascular diseases in patients with reduced function of thyroid gland.

Other literature [7, 8] also revealed that homocysteine (HCy) level is increased in patients with hypothyroidism. The authors suggested that HHCy can promote atherogenesis by increasing monocytes reactivity to inflammatory stimuli and induction of oxidative stress.

In the previous study we proved that experimental reproduction of hypothyroidism by injecting mercazolil to animals is accompanied by increase of cysteine levels, HCy and decrease of hydrogen sulfide (H_2S) concentration in blood [9]. The aim of this study was to investigate the influence of thyroid gland functional state on the main enzyme systems of sulphur-containing amino acids metabolism in liver and kidneys of experimental animals.

Material and methods.The experiments were performed on forty white nonlinear male rats (Rattus Norvegicus) weighing 150-180 g. All the animals were kept in standard vivarium conditions of 12-hour day/night mode, water and balanced granulated food were provided ad libitum. Animals were housed in sets of eight per cage in a controlled environment where food and water were provided ad libitum. All experiments were conducted in accordance with the European Communities Council Directive of 24 November 1986 for Care and Use of Laboratory Animals (86/609/EEC), and approved by the Local Ethics Committee.

Rats were assigned to one of five groups (8 animals each): the 1st – control. This group of animals got intragastric solution of 1% starch gel; the 2nd – the rats, which were injected with L-thyroxine (Berlin-Chemie AG, Germany) daily 1 time per day intragastrically during 14 days at 200 mcg/kg of weight in 1% starch gel; the 3rd – the animals treated with L-thyroxine as the previous group during 21 days; the 4th – the rats, which were injected with mercazolil (OCLtd Pharmaceutical company "Zdorovie", Ukraine) daily 1 time per day intragastrically during 14 days at 10 mcg/kg of weight in 1% starch gel; the 5th – the animals receiving mercazolil according to the above-mentioned scheme during 21 days. All the manipulations were performed under standard conditions from 9 till 10 a.m. In 24 hours after the last injection the animals were mortified by the method of cervical dislocation.

To confirm the state of hyper- and hypothyroidism, in the blood serum the levels of free thyroxine (fT_4), free triiodothyronine (fT_3) and thyroid stimulating hormone (TSH) were determined by enzyme immunoassay using the kits (Diagnostic systems, Russia) in accordance with the instructions of the manufacturer.

In the blood serum we determined total content of HCy by ELISA using the set (Axis-Shield, UK), and total cysteine (the sum of cysteine and cystine) by reaction of ninhydrine reagent in acidic medium [10]. The content of hydrogen sulfide in the environment was established by the reaction of N,N-dimethyl-para-phenylenediamine in the presence of $FeCl_3$ [11].

Liver and kidneys were perfused with cold 1.15% solution of potassium chloride and homogenized at 3000 rpm (Teflon-glass) in the environment of 1.15% potassium chloride (ratio 1:3). The homogenates were centrifuged for 30 min at 600 g and +4°C, post-nuclear supernatant aliquots were selected, in which the activity of enzymes that ensure the processes of remethylation, transsulfuration and desulfuration was determined. The functioning of remethylation cycle was assessed by the activity of the following enzymes: S-adenosylmethionine syntase (S-AMS, EC 2.5.1.6), which was defined by growth of inorganic phosphate, which is formed in ATP hydrolysis and its interaction with methionine [12]; S-adenosylhomocysteine hydrolase (S-AHH, EC 3.3.1.1) was determined by the increase of sulfhydryl groups in the reaction of S-adenosylhomocysteine hydrolysis [13]; betaine-homocysteine methyltransferase (BHMT, EC 2.1.1.5) – was determined by reduction of sulfhydryl groups in the reaction of homocysteine with betaine [14]. The processes of transsulfuration were assessed by cystathionine synthase activity of cystathionine-β-synthase (CBS, EC 4.2.1.22), which was identified by the formation of cystathionine in the reaction of condensation of homocysteine with serine [15] and by cystathionase activity of cystathionine-γ-lyase (CSE, EC 4.4.1.1), which was measured by the formation of cysteine in the reaction of cystathionine decomposition [16]. The status of desulfuration processes in liver and kidneys was

Table 1. The concentration of free thyroxine, triiodothyronine and thyroid stimulating hormone in serum of the rats with hyper- and hypothyroidism (M±m)

Index	Group of animals				
	Control	L- thyroxine		Mercazolil	
		Time from the beginning of drug administration (days)			
		14	21	14	21
fT_4, pmol/l	11.07±0.47	20.23±2.10*	26.12±1.85*	6.84±0.27*	4.25±0.42*
fT_3, pmol/l	2.58±0.24	2.70±0.18	2.88±0.21	0.87±0.06*	0.67±0.04*
TSH, mIU/L	0.34±0.03	0.15±0.02*	0.08±0.01*	0.54±0.05*	2.21±0.16*

** – changes are reliable relatively to the indicators of the control group animals, p<0.05.*

assessed by the activity of CBS, CSE and cysteine aminotransferase (CAT, EC 2.6.1.3), which was identified by the formation of H_2S in the reaction with N,N-dimethyl-paraphenylenediamine. In order to determine the activity of these enzymes the composition of the incubation media was selected, which allowed to estimate maximum H_2S formation in the respective reactions [17]. Protein content was determined by microbiuretic assay [18]. Statistical analysis was performed using Student's t-test, data were considered to be reliable at P<0.05. The results are presented as M±m.

Results and discussion.It is established that L-thyroxine introduction to the animals resulted in a constant state of hyperthyroidism, which was confirmed by the increase of fT_4 concentration in the blood of the rats of the 2nd and 3rd groups of the animals, respectively, 83 and 136% of the control level. TSH level was decreased by 56 and 76%. The concentration of fT_3 in L-thyroxine introduction did not change (Table 1). In order to suppress the production of thyroid hormone synthesis mercazolil was used (1-methyl-2-mercaptoimidazole), its thyreostatics action mechanism is associated with the inhibition of peroxidase activity which is involved in iodination of thyronine to triiodothyronine and tetraiodthyronine.

Introduction of mercazolil for the animals during 14 days caused the decrease in the content of fT_4 in the serum by 38%, and fT_3 – 66%; administration of the drug for 21 days led to the decrease in fT_4 by 62% and fT_3 – 74%. At the same time, the concentration of TSH was increased by 59% and 550% respectively on the 14th and 21st days of the experiment.

Utilization of toxic HCy is due to two main mechanisms: remethylation and transsulfuration. Remethylation cycle ensures methionine formation of HCy. Direct conversion of HCy into methionine is catalysed either by B_{12}-dependent enzyme methionine synthase, for which 5-methyltetrahydrofolate is a methyl group donor, or by folat-independent enzyme betaine-homocysteinemethyltransferase, for which betaine is the donor of methyl groups.

Another way of HCy utilization is its conversion to cysteine in the reactions of transsulfuration. In this chain, firstly HCy under the influence of CBS enzyme condenses with serine with the formation of cystationin, and then the last is decomposited by CSE to cysteine, a-ketobutyrate and ammonia.

Some time ago a desulfurize way of cysteine exchange was discovered, which is associated with production of an important regulatory gas molecule – hydrogen sulfide. Three enzymes are involved in desulfuration of cysteine with the formation of H_2S – CBS, CSE and CAT [19].

It is established that experimental hyperthyroidism is accompanied by the increased activity of remethylation cycle enzymes – BHMT, S-AMS, and S-AHH (Table 2).

Table 2. Activity of remethylation cycle enzymes in liver, kidneys of the rats with a model of hyper- and hypothyroidism (M±m)

Index	Object of the study	Control	Group of animals			
			L- thyroxine		Mercazolil	
			Time from the beginning of drug administration (days)			
			14	21	14	21
S-AMS, nmolPO_4^{3-}/min·mgprotein	Liver	5.84±0,43	6.08±0.59	7.85±0.48*	4.25±0.29*	4.02±0.43*
	Kidneys	3.04±0.27	3.93±0.36	4.96±0.28*	2.03±0.14*	1.82±0.26*
S-AHH, nmol HCy-SH/min·mgprotein	Liver	5.66±0.30	5.91±0.48	7.66±0.53*	4.80±0.42	4.28±0.32*
	Kidneys	3.83±0.36	5.18±0.59	6.08±0.50*	2.32±0.17*	2.08±0.18*
BHMT, nmolHCy-SH/min·mgprotein	Liver	8.65±0.50	11.90±0.78*	12.50±0.89*	5.60±0.43*	4.95±0.27*
	Kidneys	3.33±0.17	4.48±0.21*	4.90±0.33*	2.15±0.19*	1.76±0.14*

** – the changes are reliable relatively to the indicators of the control group of animals, p<0.05*

In both research periods under the influence of L-thyroxine the BHMT activity increased both in liver tissue (by 38% and 45%), and in kidneys (by 35% and 47%) compared to the control group of animals. Activity of S-AMS and S-AHH significantly increased in the tissues only on the 21st day of the study.

In contrast to L-thyroxine, the administration of mercazolil was accompanied by inhibition of the activity of methylation cycle enzymes in liver and kidneys (Table 2), which logically should lead to the increase in HCy amino acid content. Indeed, when administration of mercazolil during 14 days, the concentration of HCy increased by 98% (from 8.53±0.39 to 16.91±1.12 μmol/l), and during the 21st day – by 160% (to 22.20±1.39 μmol/l) (Fig. 1).

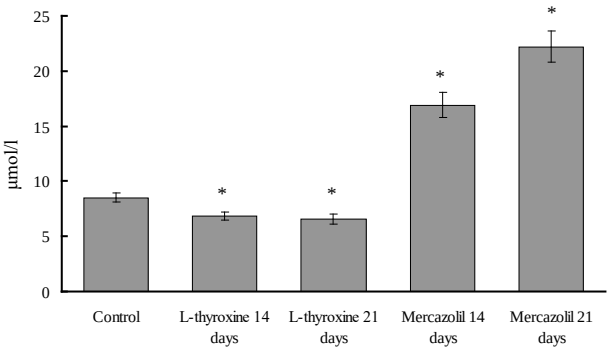

*Fig. 1. Homocysteine concentration (μmol/l) in blood serum of the rats with a model of hyper- and hypothyroidism. * – changes are reliable relatively to the indicators of the intact group animals*

When L-thyroxine administering to the animals, the HCy level in the serum decreased by 19% (from 8.53±0.39 to 6.88±0.37 μmol/l) on the 14th day and by 23% (up to 6.53±0.45 μmol/l) on the 21st day of the experiment.

Hyperthyroidism simulation led to the increase (by 35% on the 21st day) of cystationine synthase activity of CBS in liver, and hypothyroidism simulation – to decrease of this enzyme activity (by 30 and 37% respectively in liver and kidneys) (Table 3). Cystationinase activityof CSE under the influence of L-thyroxine was not changed in liver and decreased in kidney by 27% on the 21st day of the study.

The data that reflect the results of the research of influence of hyper- and hypothyroidism on cysteine desulfuration reaction is presented in Table 4. Under CBS enzyme influence the cysteine interacts with homocysteine followed by the formation of cystationine and hydrogen sulfide. This enzyme also catalyses conversion of cysteine into serine, in this process H_2S molecule is also released. L-thyroxine did not cause any changes in CBS activity in liver and led to its increase in kidneys only on the 21st day. The rate of H_2S formation from cysteine by CBS enzyme decreased in the administration of mercazolil in both studied tissues.

Another enzyme that catalyses cysteine desulfunation by conversion of the latter into pyruvate is CSE. The data in the table 4 proves that in liver of the rats, injected with L-thyroxine, the changes in CSE activity were not observed. Only the long-term (during 21 days) mercazolil injection caused a decrease in CSE activity in liver. At the same time in kidneys of the animals with hyperthyroidism, on the 21st day of the experiment, CSE activity doubled, and in the simulation of hypothyroidism – decreased during both periods of the study (by 37% and 39% respectively).

Splitting of hydrogen sulfide from cysteine can also occur under the influence of CAT enzyme, which catalyses transamination reaction of cysteine with a-ketoglutaric acid with glutamic and pyruvic acids formation. The same as in the case of CSE, the inhibitory effect of mercazolil on the activity of CAT in liver was observed which depended on the duration of drug administration, whereas L-thyroxine

*Table 3. Activity (nmol/min*mg of protein) of transsulfuration enzymes in liver and kidneys of the rats with a model of hyper- and hypothyroidism (M±m)*

Index	Object of the study	Control	Group of animals			
			L-thyroxine		Mercazolil	
			Time from the beginning of drug administration (days)			
			14	21	14	21
CBS, nmolcystationine/min·mgprotein	Liver	12.10± 0.65	14.22± 1.37	16.38± 1.21*	10.56± 0,55	8.51± 0.46*
	Kidneys	16.82± 1.33	17.28± 0.81	17.65± 1.28	14.83± 1.01	10.54± 0.86*
CSE, nmolcysteine/min·mgprotein	Liver	16.19± 1.06	17.43± 1.27	17.61± 1.30	15.21± 0.89	11.60± 1.06
	Kidneys	13.64± 0.98	16.26± 1.24	16.85± 1.28	10.13± 0.91	10.02± 0.60*

** – the changes are reliable relatively to the indicators of the control group of animals, p<0.05*

Table 4. Activity of H_2S synthesis enzymes in liver and kidneys of the rats with a model of hyper- and hypothyroidism (M±m)

Index	Object of the study	Intact	Group of animals			
			Model of hyperthyroidism		Model of hypothyroidism	
			L-thyroxine		Mercazolil	
			Time from the beginning of drug administration (days)			
			14	21	14	21
CBS, nmolH_2S/min·mgprotein	Liver	4.04±0.34	4.38±0.45	4.65±0.37	3.28±0.22	2.72±0.27*
	Kidneys	3.31±0.10	3.33±0.22	4.01±0.20*	2.70±0.18*	2.37±0.25*
CSE, nmolH_2S/min·mgprotein	Liver	4.01±0.20	4.17±0.23	4.30±0.16	3.06±0.31	2.70±0.21*
	Kidneys	0.92±0.04	1.29±0.14	1.84±0.15*	0.58±0.03*	0.56±0.03*
CAT, nmolH_2S /min·mgprotein	Liver	1.67±0.12	1.41±0.20	1.80±0.29	1.07±0.14*	1.03±0.12*
	Kidneys	1.28±0.03	1.44±0.08	1.43±0.10	1.20±0.10	1.04±0.07*

** – the changes are reliable relatively to the indicators of the control group of animals, p<0.05*

had no effect on enzyme activity. In kidneys CAT activity changed significantly under the influence of mercazolil only in long-term use.

Thus, we can draw a conclusion that the state of long-term hypothyroidism causes inhibition of processes of hydrogen sulfide formation in the organs of experimental animals (in liver and kidneys desulfuration activity of CBS, CSE and CAT are decreased). However, the prolonged use of L-thyroxine led to increase in desulfuration activity of CBS and CSE in kidneys. These changes in the activity of these enzymes bound to affect the content of H_2S in blood of the animals with hyper- or hypothyroidism.

As presented in Figure 2, the administration of mercazolil to animals during 14 days led to H_2S level decrease by 17% (from 88.02±4.01 to 72.9±3.04 μmol/l). Further administration of the drug, H_2S content continued to decrease and reached the level of 66.9±4.39 μmol/l on the 21st day of the experiment. So, hypothyroidism conditions in the body decrease the production of important regulatory gas molecule of hydrogen sulfide, which has vasodilatory properties and inhibits platelet aggregation.

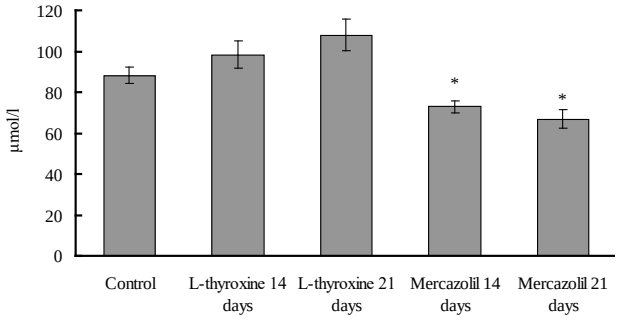

*Fig. 2. H_2S concentration (μmol/l) in blood serum of the rats with a model of hyper- and hypothyroidism. * – changes are reliable relatively to the indicators of the intact group animals*

It is obvious that the suppression of cysteine utilization ways (desulfurizing reactions) under the influence of mercazolil resulted in the increase in this amino acid content from 111.5±6.61 μmol/l in the intact animals to 138.49±7.55 and 155.54±8.30 μmol/l in the rats of the 4th and 5th groups respectively (Fig. 3).

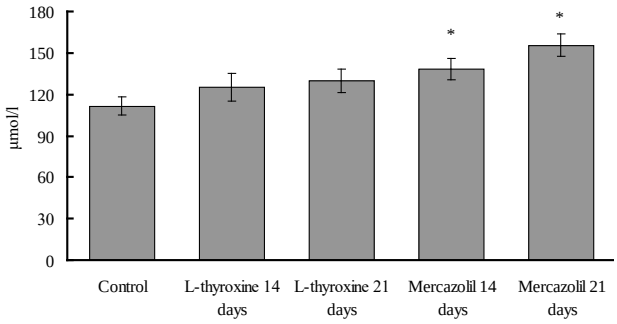

*Fig. 3. Cysteine concentration (μmol/l) in blood serum of the rats with a model of hyper- and hypothyroidism. * – changes are reliable relatively to the indicators of the intact group animals*

Thus, experimental hypothyroidism is accompanied by significant changes in the content of homocysteine and hydrogen sulfide in serum: two molecules that play an important role in the pathogenesis of cardiovascular diseases such as atherosclerosis, arterial hypertension, propensity to thrombosis. As it follows from our experiments, the increase of homocysteine concentration in blood of the rats with hypothyroidism is the consequence of methylation cycle reactions failure and inhibition of transsulfuration processes in liver and kidneys.

In its turn, hydrogen sulfide level decrease is caused by the inhibition of cysteine desulfuration reactions (decrease in the activity of cystathionine-β-synthase, cystathionine-γ-lyase and cysteine aminotransferase). We can assume that cardiovascular complications, which often occur in patients

with hypothyroidism, may at least partially be caused by the decreased functioning of sulphur-containing amino acids metabolism ways and, as a consequence, increased levels of homocysteine and lower concentrations of hydrogen sulfide in serum.

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SUMMARY

SULPHUR-CONTAINING AMINO ACIDS METABOLISM IN EXPERIMENTAL HYPER- AND HYPOTHYROIDISM IN RATS

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Hyper- and hypothyroidism are some of the most common endocrinopathies that cause many metabolic disorders including amino acids metabolism. However, a specific molecular mechanism of thyroid hormones influence on sulphur-containing amino acids metabolism has not been established.

The aim of our research was to investigate experimentally the influence of thyroid gland functional state on the main enzymatic systems of sulphur-containing amino acids metabolism in liver and kidneys, the content of homocysteine, cysteine and H_2S in blood. The rats were administered with L-thyroxine and mercazolil to simulate the states of hyper- and hypothyroidism, which were confirmed by the content of fT_3, fT_4 and TSH in the blood.

In liver and kidneys of the animals with hypothyroidism we observed the decrease in the activity of enzymes of remethylation cycle of S-adenosylmethioninsyntase, S-adenosylhomocysteinhyhdrolase, betaine-homocysteine methyltransferase. Suppression of transsulfuration transformation of homocysteine to cysteine in hypothyroidism was mainly due to the inhibition of cystathionine synthase activity of cystathionine-β-synthase, wherein cystathionase activity of cystathionine-γ-lyase was not changed.

In animals with hypothyroidism we also noticed the inhibition of cysteine desulfunation reactions: the activity of enzymes of cystathionine-β-synthase, cystathionine-γ-lyase and cysteine aminotransferase significantly decreased in liver and kidneys.

Experimental hyperthyroidism was accompanied

by increase in activity of remethylation cycle enzymes, increase in cystationine synthase activity of cystathionine-β-synthase in liver and activity of these enzymes in kidneys.

The simulation of hyperthyroidism led to the decrease of homocysteine concentration, and of hypothyroidism – to the increase of homocysteine and cysteine concentrations and reduced H_2S content in blood of the animals.

Thus, the significant risk factors for the development of atherosclerosis, endothelial dysfunction and hypercoagulation in hypothyroid conditions may be the disorders in the processes of remethylation, transsulfuration, and desulfuration of sulphur-containing amino acids in organs.

Keywords: thyroid hormones, homocysteine, cysteine, hydrogen sulfide, remethylation, transsulfuration, desulfuration.

РЕЗЮМЕ

ОСОБЕННОСТИ ОБМЕНА СЕРОСОДЕРЖАЩИХ АМИНОКИСЛОТ ПРИ ЭКСПЕРИМЕНТАЛЬНОМ ГИПЕР- И ГИПОТИРЕОЗЕ У КРЫС

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Гипер- и гипотиреоз - распространенные эндокринопатии, приводящие ко многим метаболическим нарушениям, в том числе и в обмене аминокислот. Однако, конкретные молекулярные механизмы влияния тиреоидных гормонов на обмен серосодержащих аминокислот по сей день неизучены.

Целью исследования явилось определить влияние функционального состояния щитовидной железы на основные ферментные системы метаболизма серосодержащих аминокислот в печени и почках, содержание гомоцистеина, цистеина и H_2S в крови в эксперименте.

40 белым нелинейным крысам-самцам весом 150-180 гр вводили L-тироксин и мерказолил для моделирования состояний гипер- и гипотиреоза, которые подтверждались показателями cT_3, cT_4 и ТТГ в крови.

В печени и почках животных с гипотиреозом наблюдалось снижение активности ферментов цикла реметилирования - S-аденозилметионинсинтетазы, S-аденозилгомоцистеингидролазы, бетаингомоцистеин-метилтрансферазы. Подавление транссульфуразного пути превращения гомоцистеина в цистеин при гипотиреозе происходило, в основном, за счет ингибирования цистатионинсинтазной активности цистационин-β-синтазы, при этом цистатионазная активность цистатионин-γ-лиазы не изменялась. У животных с гипотиреозом наблюдали угнетение реакции десульфуруривания цистеина - достоверно снижалась активность цистатионин-β-синтазы, цистатионин-γ-лиазы и цистеинаминотрансферазы в печени и почках.

Экспериментальный гипертиреоз сопровождался увеличением активности энзимов цикла реметилирования, повышением цистатионинсинтазной активности цистатионин-β-синтазы в печени и активности как цистатионин-β-синтазы, так и цистатионин-γ-лиазы в почках.

Моделирование гипертиреоза приводило к снижению концентрации гомоцистеина, а гипотиреоза - повышению концентраций гомоцистеина и цистеина и снижению содержания H_2S в крови животных.

Авторами делаестя вывод, что весомыми факторами риска развития атеросклероза, эндотелиальной дисфункции и гиперкоагуляции при гипотиреоидном состоянии, по всей вероятности, является нарушение процессов реметилирования, трансульфурирования и десульфурирования серосодержащих аминокислот в органах.

რეზიუმე

გოგირდისშემცველი ამინომჟავების ცვლის თავისებურება ექსპერიმენტული ჰიპერ- და ჰიპოთირეოზის დროს ვირთაგვებში

[1]ვ. ნეჩიპორუკი, [1]ნ. ზაიჩკო, [2]მ. კორდა, [1]ა. მელნიკი [1]ე. კოლოშკო

[1]ვინიცის ნ. პიროგოვის სახ. ეროვნული სამედიცინო უნივერსიტეტი; [2]ტერნოპოლის ი. გორბაჩევსკის სახ. სახელმწიფო უნივერსიტეტი, უკრაინა

ჰიპერ- და ჰიპოთირეოზი საკმაოდ გავრცელებული ენდოკრინოპათოლოგიებია, რომლებიც იწვევენ მეტაბოლურ დარღვევებს, მათ რიცხვში ამინომჟავების ცვლაში. უნდა აღინიშნოს, რომ თირეოიდული ჰორმონების კონკრეტული მოლეკულური მექანიზმების გავლენა გოგირდისშემცველი ამინომჟავების ცვლაზე სადღეისოდ არ არის სათანადოთ შესწავლილი.

კვლევის მიზანს წარმოადგენდა ფარისებრი ჯირკვლის ფუნქციური მდგომარეობის ზეგავლენის განსაზღვრა გოგირდისშემცველი ამინომჟავების მეტაბოლიზმის ძირითად ფერმენტულ სისტემაზე ღვიძლში და თირკმელებში, ასევე, ჰომოცისტეინის, ცისტეინისა და H_2S შემცველობაზე სისხლში, ექსპერიმენტში.

150-180 გრ წონის 40 არახაზოვან თეთრ ვირთაგვებში შეჰყავდათ L-ტიროქსინი და მერკაზოლილი ჰიპერ- და ჰიპოთირეოზის მოდელირების მიზნით, რაც შემდეგ დასტურდებოდა სისხლში fT_3, fT_4 და TSH მაჩვენებლებით.

ცხოველებს ჰიპოთირეოზით ღვიძლში და თირკმელებში აღენიშნებოდა S-ადენოზილმეტიონინსინთაზის, S-ადენოზილგომოცისტეინჰიდროლაზის, ბეტაინჰომოცისტეინმეტილტრანსფერაზის

ციკლის ფერმენტების აქტივობის დაქვეითება. ჰომოცისტეინის ცისტეინში გარდაქმნის ტრანსსულფურაზული გზის დათრგუნვა ჰიპოთირეოზის დროს, ძირითადად, ხდებოდა ცისტაციონინ–β-სინთაზის ცისტაციონინსინთაზური აქტივობის ინჰიბირების ხარჯზე, ამავდროს ცისტაციონინ-γ-ლიაზის ცისტაციონაზური აქტივობა არ იცვლებოდა. ცხოველებს ჰიპოთირეოზით აღენიშნებოდათ ცისტეინის დისულფურიების რეაქციის დათრგუნვა – ღვიძლში და თირკმელებში ცისტაციონინ–β-სინთაზის, ცისტაციონინ-γ-ლიაზის და ცისტეინამინოტრანსფერაზის სარწმუნო დაქვეითება.

ექსპერიმენტულ ჰიპოთირეოზს თან ახლდა რემეთილირების ციკლის ენზიმების აქტივობის მატება,ღვიძლში ცისტაციონინ–β-სინთაზის ცისტაციონინსინთაზური აქტივობის, ხოლო თირკმელებში როგორც ცისტაციონინ–β-სინთაზას, ასევე, ცისტაციონინ-γ-ლიაზის აქტივობის ზრდა. ჰიპერთირეოზის მოდელირება იწვევდა ჰომოცისტეინის კონცენტრაციის დაქვეითებას, ხოლო ჰიპოთირიოზის – ჰომოცისტეინის და ცისტეინის კონცენტრაციის მატებას და H_2S შემცველობის დაქვეითებას ცხოველების სისხლში.

ავოტერების მიერ გამოტანილია დასკვნა,რომ ჰიპოთიროიდული მდგომარეობის პირობებში ათეროსკლეროზის, ენდოთელური დისფუნქციის და ჰიპერკოაგულაციის განვითარების მნიშვნელოვან რიკს-ფაქტორს წარმოადგენს გოგირდისშემცველი ამინომჟავების რემეთილირების, ტრანსულფურირების და დისულფურირების პროცესების დარღვევა ორგანოებში.

VITAMINS C AND E COMBINED EFFECT ON THE RAT MYOCARDIUM UNDER ALLOXAN-INDUCED DIABETES

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Diabetes mellitus represents a significant medico-biological problem in the entire world. It is a heavy burden on the economy, health system and society. According to the data of the World Health Organization (WHO), by 2014, the number of diabetics in the age group of over 18 years increased by 9% [5]. It also reported that 1.5 million people died due to diabetes and its complications in 2012 [11]. Based on data of the International Diabetes Federation (IDF) only in Europe during 2015 approximately 627 133 people at the age of 20-79 years died due to diabetes, where the male-female ratio was the following: 314 701 - 312 432.

Type 1 diabetes is a chronic, autoimmune disease, incompletely studied in immunological, genetic and environmental terms. In type 1 diabetes the immune response is stimulated toward the antigenic properties of the β- cells, followed by the irreversible structural and functional decomposition of pancreatic β- cells [2].

It is commonly known, that du to diabetes mellitus the risk of cardiovascular diseases and mortality increases [3]. The epidemiological and clinical data for the last two decades show that diabetes mellitus increases the risk of so-called «diabetic cardiomyopathy», which in turn is not dependent on other factors, in particular such as ischemic heart disease and arterial hypertension [4]. Various mechanisms are activated in hyperglycemia, which lead to oxidative stress, endothelial dysfunction and atherosclerotic changes. The changes, developed in cardiovascular system in diabetes, are mainly linked to glycation processes. The high levels of the glycation final products, oxidation of proteins and lipids, non-enzymatic glycosylation and generation of active forms of oxygen contribute to cell damage [6,7,8], including complications in the myocardium and its blood vessels. Reasoning from the above mentioned, the aim of the research was to study changes in the myocardium and its microcilculatory network at the early stage of experimental diabetes and they changes under to use the combined impact of powerful antioxidants (Vitamin C and Vitamin E) on the rat myocardium in conditions of alloxan-induced diabetes.

Vitamin C

VitaminC (Ascorbic acid) is a low molecular weight, water-soluble antioxidant, which is not synthesized and it does not have a depot in the body. This is most important antioxidant- vitamin in the interstitial fluid. Vitamin C was isolated for the first time in 1923 - 1927 from lemon juice by S.S. Zilva. It is known that Vitamin C is a powerful antioxidant and characterized by multilateral activity: supports the absorption of carbohydrates and proteins, absorption of iron from food, participates in blood coagulation and metabolic processes; provides generation of energy at the cellular level,to participates in ATP synthesis. It is determined that it reduces the level of cholesterol in the blood and assists in normalization of blood pressure; reduces the