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INFLUENCE OF AMMONIUM PYRROLIDINEDITHIOCARBAMATE ADMINISTRATION ON THE DEVELOPMENT OF OXIDATIVE STRESS IN RAT HEART ON THE BACKGROUND OF METABOLIC SYNDROME MODELING

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Metabolic syndrome, despite being a disease of non-infectious origin, is often accompanied by inflammation induced by metabolic disorders (meta-inflammation). The purpose of this work is to determine the activity of antioxidant enzymes, the production of superoxide anion radical, the content of oxidatively modified proteins and the concentration of malondialdehyde in the heart of rats under conditions of experimental metabolic syndrome and ammonium pyrrolidine dithiocarbamate administration. The study was conducted on 24 mature male Wistar rats weighing 200-260 g. The animals were divided into 4 groups of 6 animals each: control group; metabolic syndrome group (metabolic syndrome was reproduced by using a 20 % fructose solution as the only source of water for 60 days); ammonium pyrrolidinedithiocarbamate administration group (i.p. 76 mg/kg thrice a week for 60 days), and group of ammonium pyrrolidinedithiocarbamate administration on the background of metabolic syndrome modeling. Metabolic syndrome leads to development of oxidative stress in rat heart, which is characterized by excessive production of reactive oxygen species and insufficiency of antioxidant defense. Ammonium pyrrolidine dithiocarbamate administration decreased superoxide production by 55.44 %, increased superoxide dismutase and catalase activity by 156.32 % and 111.44 %, respectively, and decreased concentration of malondialdehyde by 22.41 %. Administration of blocker of NF-κB activation (ammonium pyrrolidinedithiocarbamate) during modeling of metabolic syndrome limits excessive production of reactive oxygen species and intensity of lipid peroxidation, while increasing antioxidant defense of rat heart.

Key words: metabolic syndrome, heart, NF-κB, ammonium pyrrolidinedithiocarbamate, oxidative stress.

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ВПЛИВ АМОНІЮ ПІРОЛІДИНДИТІОКАРБАМАТУ НА РОЗВИТОК ОКСИДАТИВНОГО СТРЕСУ У СЕРЦІ ЩУРІВ ЗА УМОВ МОДЕЛЮВАННЯ МЕТАБОЛІЧНОГО СИНДРОМУ

Метаболічний синдром, незважаючи на те, що він є захворюванням неінфекційного походження, часто супроводжується запаленням, спричиненим порушенням обміну речовин (метазапалення). Мета роботи – визначити активність антиоксидантних ферментів, продукцію супероксидного аніон-радикала, вміст окисно-модифікованих білків та концентрацію малонового діальдегіду в серці щурів за умов експериментального метаболічного синдрому та введення амонію піролідиндитіокарбамату. Дослідження проводили на 24 статевозрілих самцях щурів лінії Вістар масою 200-260 г. Тварини були розподілені на 4 групи по 6 тварин у кожній: контрольна; група метаболічного синдрому (метаболічний синдром відтворювався шляхом використання 20 % розчину фруктози як єдиного джерела води протягом 60 днів); група введення піролідиндитіокарбамату амонію (в/о 76 мг/кг 3 рази на тиждень протягом 60 днів) та група введення піролідиндитіокарбамату амонію на тлі моделювання метаболічного синдрому. Метаболічний синдром призводить до розвитку оксидативного стресу в серці щурів, який характеризується надмірною продукцією активних форм кисню та недостатністю антиоксидантного захисту. Введення амонію піролідиндитіокарбамату знизило продукцію супероксиду на 55,44 %, підвищило активність СОД і каталази на 156,32 % і 111,44 % відповідно, а також знизило концентрацію малонового діальдегіду на 22,41 %. Застосування блокатора активації NF-κB (амонію піролідиндитіокарбамату) при моделюванні метаболічного синдрому обмежує надлишкову продукцію активних форм кисню та інтенсивність перекисного окислення ліпідів, одночасно підвищуючи антиоксидантний захист серця щурів.

Ключові слова: метаболічний синдром, серце, NF-κB, амоній піролідиндитіокарбамат, оксидативний стрес

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Metabolic syndrome (MetS), despite being a disease of non-infectious origin, is often accompanied by inflammation induced by metabolic disorders (meta-inflammation). Inflammation caused by metabolic syndrome development harbors systemic influence and is usually accompanied by increase in blood of tumor necrosis factor alpha (TNF-α), interleukin 1 (IL-1), interleukin 6 (IL-6) and other inflammatory mediators [14]. Elevation of abovementioned inflammatory mediators in blood leads to development of oxidative stress in various organs and tissues [8]. Oxidative stress development caused by MetS is one of the key pathogenetic mechanisms leading to cardio-vascular complications of MetS [6].

Expression of cytokine genes is a closely regulated process controlled by several pro- and anti-inflammatory transcriptional factors like: nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), signal transducer and activator of transcription 3 (STAT 3), activator protein 1 (AP 1) and others. Transcription factor NF-κB is one of the key players in development of inflammatory response and is responsible for control over cellular redox homeostasis. NF-κB can increase reactive oxygen (ROS) and reactive nitrogen (RNS) species formation by directly controlling the expression of such enzymes as inducible nitric oxide synthase (NOS) and phagocyte NADPH-oxidase. Excessive activation of NF-κB impairs mitochondrial respiration leading to increase ROS formation and decrease in ATP synthesis. Scientific literature provides evidence regarding activation of transcription factor NF-κB during MetS [1]. Clinical medicine also provides information that treatment of MetS with drugs influencing NF-κB activation, such as Metformin, has positive outcomes [12]. However, Metformin is a biguanide and besides influence on NF-κB activation also has stimulating effect on adenosine mono phosphate kinase (AMPK) cascade and several others.

It is still under much scientific debate whether selective blockade of activation of transcription factor NF-κB is a safe therapeutic approach to treatment and prevention of metabolic syndrome development caused by excessive calorie intake.

The purpose of the study was to determine the activity of antioxidant enzymes, the production of superoxide anion radical, the content of oxidatively modified proteins and the concentration of malondialdehyde in the heart of rats under conditions of experimental metabolic syndrome and ammonium pyrrolidine dithiocarbamate administration.

Materials and methods. The study was conducted on 24 mature male Wistar rats weighing 200–260 g. The animals were randomly divided into 4 groups of 6 animals each. The first group was a control group, the animals of this group received manipulations similar to those of the other groups, but instead of the active substances, they received a 0.9 % solution of sodium chloride. The second group was the experimental metabolic syndrome group (MetS group). MetS was reproduced by using a 20 % fructose solution as the only source of water for 60 days [10]. The third group was ammonium pyrrolidinedithiocarbamate (PDTC) administration group (PDTC group). Rats from this group received intraperitoneal injection of PDTC at a dose 76 mg/kg thrice a week for 60 days [13]. The fourth group was the group of the combined effect of PDTC administration and reproduction of MetS (PDTC+MetS group). Animals of this group received a 20 % fructose solution as the only source of water and were administered PDTC according to the scheme of group 3. Experiment lasted for 60 days.

Authors received approval from Bioethical Committee of Poltava State Medical University (Record No. 206 from 24.06.2022) for manipulations with laboratory animals. All manipulations with laboratory animals were performed in strict accordance with international and local legislation on Bioethics.

The object of the study was a 10 % homogenate of rat heart. We studied basic SAR production, SAR production from microsomal electron transport chain (ETC), superoxide anion radical (SAR) production from mitochondrial ETC using reduced nitroblue tetrazolium method [13]. The activity of superoxide dismutase (SOD, EC 1.15.1.1) was determined by the rate of inhibition of autoxidation of adrenaline in the presence of the sample. Catalase activity (EC 1.11.1.6) was determined by the rate of splitting of hydrogen peroxide in the presence of the sample [13]. The concentration of free malondialdehyde (MDA) was determined by the formation of a colored reaction product between MDA and 1-methyl-2-phenylindole [13]. The concentration of oxidatively modified proteins (OMP) was determined by determining carbonyl groups, which are formed during the interaction of reactive oxygen species with amino acid residues using 2,4-dinitrophenylhydrazine [13].

The statistical significance of the difference between groups was determined using the non-parametric Kruskal-Wallis analysis of variance method, followed by pairwise comparisons using the Mann-Whitney U-test. The difference was considered statistically significant at $p<0.05$. To avoid multiple comparisons error we used correction by Bonferroni method. Data was represented in tables as mean ± standard error of mean (M±SE).

Results of the study and their discussion. MetS modelling increased the basic production of SAR, its production mitochondrial and microsomal ETCs in rat heart compared to the control group of animals, thus leading to excessive ROS formation (Tab. 1). SOD activity and catalase decreased compared to the control group of animals, indicating drop in antioxidant protection. The concentration of MDA and the content of OMP in the heart of rats in the MetS group increased compared to the control group of animals, evidencing about oxidative damage to cellular membranes and proteins.

Table 1

Parameters of the pro- and antioxidant balance in the heart of rats under the condition of modeling the metabolic syndrome and ammonium pyrrolidinedithiocarbamate administration (M±m)

Parameters	Groups			
	Control, n=6	MetS, n=6	PDTC, n=6	PDTC+MetS, n=6
SAR production, nmol/s per g				
Basic	0.48±0.03	1.93±0.07*	0.66±0.03 */#	0.86±0.05 */#/^
From microsomal ETC	10.57±0.14	12.72±0.36*	10.39±0.29 #	11.50±0.07 */#/^
From mitochondrial ETC	12.11±0.18	15.66±0.06*	11.82±0.17 #	13.16±0.14 */#/^
SOD activity, c.u.	8.28±0.44	5.54±0.37*	9.35±0.32 #	14.20±1.09 */#/^
Catalase activity, μkatal/g	0.84±0.01	0.577±0.001*	0.89±0.01 */#	1.22±0.02 */#/^
Free MDA concentration, μmol/g	9.67±0.21	19.77±0.22*	12.66±0.57 */#	15.34±0.48 */#/^
OMP content, c.u.	0.085±0.001	0.140±0.011*	0.095±0.005 #	0.108±0.008 */#

Note: * - data is statistically significantly different from control group ($p<0.05$). # - data is statistically significantly different from MetS group ($p<0.05$). ^ - data is statistically significantly different from PDTC group ($p<0.05$).

In PDTC group basic production of SAR in rat heart increased by 37.50 % compared to the control group. SAR production from mitochondrial and miscrosomal ETCs in the heart of rats in the PDTC group of animals did not change compared to the control group of animals. SOD activity in rat heart in the PDTC group did not change, while catalase activity increased by 5.95 % compared to the control group of animals. The concentration of MDA in rat heart in the PDTC group increased by 30.92 %, while the content of OMP did not change compared to the control group. Basic production of SAR in rat heart in PDTC group decreased by 65.80 %, from microsomal ETC by 18.32 %, from mitochondrial ETC by 24.52 % compared to the MetS group. SOD activity in rat heart in PDTC group increased by 68.77 %, catalase activity by 54.25 % compared to the MetS group. MDA and OMP concentration in rat heart decreased by 35.96 % and 32.14 %, respectively, compared to MetS group.

Administration of PDTC against the background of MetS modelling led to an increase in the basic production of SAR in rat heart by 79.17 % when compared with the control group of animals. SAR production from microsomal ETC in rat heart in PDTC+MetS group increased by 8.80 %, from mitochondrial ETC by 8.67 % compared to the control group of animals. The activity of SOD in rat heart in PDTC+MetS group increased by 71.50 %, the activity of catalase increased by 45.24 % compared to the control group of animals. The concentration of MDA in rat heart in PDTC+MetS group increased by 58.63 %, and the content of OMP increased by 27.06 % compared to the control group of animals.

In PDTC+MetS group basic production of SAR in rat heart decreased by 55.44 %, SAR production from microsomal ETC decreased by 9.59 %, from mitochondrial ETC it decreased by 15.96 % compared to the MetS group. The activity of SOD in rat heart in PDTC+MetS group increased by 156.32 % and the activity of catalase by 111.44 % compared to the MetS group. The concentration of MDA in rat heart in PDTC+MetS group decreased by 22.41 %, and the content of OMP decreased by 22.86 % compared to the MetS group.

The basic production of SAR in rat heart in PDTC+MetS group increased by 30.30 % compared to PDTC group. The production of SAR from microsomal and mitochondrial ETCs increased by 10.68 % and 11.34 %, respectively, compared to the PDTC group. The activity of SOD in rat heart in PDTC+MetS group increased by 51.87 % and catalase activity increased by 37.08 % compared to the PDTC group. The concentration of MDA in rat heart in the PDTC+MetS group increased by 21.17 %, and the OMP content did not change compared to the PDTC group.

Development of oxidative stress in various organs and tissues during metabolic syndrome is one of the hallmarks of its progression and its development may indicate the possibility of aggravation of metabolic syndrome by type 2 diabetes mellitus. Several mechanisms of oxidative stress development during MetS were proposed [11, 15]. Among them special notion should be given to activation of nicotinamide adenine dinucleotide phosphate oxidases (EC 1.6.3.1, NOX), a group of oxidases consisting from several iso-enzymes. These enzymes convert high energy containing substrate (reduced nicotinamide adenine dinucleotide phosphate, NADPh+H) to superoxide ($O_2^{\bullet-}$), which is then usually used for oxidation of metabolic substrates or antibacterial action of phagocytes [11]. Overactivation of second isoform of NOX (NOX-2) is responsible for adverse effects on mitochondria caused by MetS, because NOX-2 depletes nicotinamide adenine dinucleotide supply and causes excessive SAR formation [11]. Credibility of such mechanism in our research is supported by increased SAR production from mitochondrial ETC. Another possible mechanism of increased ROS production during MetS is development of endoplasmic reticulum stress (ER-stress) [11]. Increased production of SAR due to ER-stress is supported by increase of SAR production from microsomal ETC observed in our study. Most of abovementioned mechanisms of

increased ROS production during MetS development are closely regulated by activation of transcription factor NF-κB [2]. A decrease in activity of antioxidant enzymes observed in our study can be connected to competition for the DNA binding site between NF-κB and nuclear factor erythroid 2-related factor 2 (Nrf-2), under direct transcriptional control of which are enzymes like SOD and catalase studied in our research [7]. An increase in lipid peroxidation, evidenced by elevated MDA concentration observed in our study, and heightened intensity of protein damage are a logical result of the increased ROS production and inadequate antioxidant protection caused by MetS modelling.

PDTC is a potent blocker of activation of transcription factor NF-κB, which was evidenced by several researches [9, 13]. A decrease in ROS production may be connected to absence of stimulating influence of activation of transcription factor NF-κB on abovementioned mechanisms of its production. This suggestion is supported by our research results, which show a decrease in ROS production from microsomal and mitochondrial ETCs in PDTC+MetS group compared to MetS group. An increased activity of antioxidant enzymes may be caused by reduction of competition between NF-κB and Nrf-2 for the DNA binding site due to blockade of NF-κB activation by PDTC administration [7]. Therefore, blockade of NF-κB activation by PDTC administration is the main mechanism, which leads to decrease in lipid peroxidation and intensity of protein damage observed in PDTC+MetS group compared to MetS group.

An increase in basic superoxide production caused PDTC administration to animals without dietary changes necessary for metabolic syndrome development may be connected not to the PDTC's ability to influence NF-κB activation, but with PDTC's chemical properties. Ammonium pyrrolidinedithiocarbamate is a potent chelator agent in regards of Cu^{2+} and Zn^{2+} ions [5]. It should be mentioned, that both Cu^{2+} and Zn^{2+} ions have a pathogenetic connection to MetS and type 2 diabetes. For instance, Zn^{2+} ions can prolong insulin action and increase insulin sensitivity, while excessive amount of copper ions can cause oxidative stress development [3]. On the other hand, copper deficiency can impair antioxidant defense due to chelation of Cu^{2+} ions in superoxide dismutase 1 (SOD1), thus lowering its activity [4]. Interestingly, in our research we discovered, that in PDTC group total SOD activity was not different compared to control group, but we observed increase in lipid peroxidation and catalase activity. Further studies are necessary to evaluate possible mechanisms of PDTC toxicity before it can be considered a safe treatment option for MetS.

Conclusion

Metabolic syndrome leads to development of oxidative stress in rat heart, which is characterized by excessive production of reactive oxygen species and insufficiency of antioxidant defense.

Administration of blocker of NF-κB activation (ammonium pyrrolidinedithiocarbamate) during modeling of metabolic syndrome limits excessive production of reactive oxygen species and intensity of lipid peroxidation, while increasing antioxidant defense of rat heart.

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MORPHOLOGICAL CHARACTERISTICS OF RAT BRONCHI AGAINST THE BACKGROUND OF POST-TRAUMATIC STRESS DISORDER AND AFTER QUERCETIN CORRECTION

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War affects the daily lives of the vast majority of Ukrainians. Therefore, post-traumatic stress disorder has become one of the most pressing medical and social problems in Ukraine today. It is characterised by a complex pathogenesis and comorbidity with many other diseases. Studying models of post-traumatic stress disorder in rats, its impact on various organs and systems, as well as finding ways to correct it are crucial for restoring the health of victims. The work presents the results of a morphological study of the effect of post-traumatic stress disorder on the rat bronchi and its correction with quercetin. It has been established that this disorder causes significant destructive changes in the large bronchi of rats, in particular, desquamation of epithelial cells with the formation of cellular detritus in the bronchial lumen, hyperhydration and leukocyte infiltration of the mucosa and submucosa, and haemomicrocirculation disorders. Intraperitoneal injection of water-soluble quercetin complex once a day for seven days in rats significantly reduced the damage to the large bronchi against the background of post-stress disorder, indicating this agent's effectiveness as a stress protector.

Key words: post-traumatic stress disorder, bronchi, lungs, histological changes, morphological changes, correction.

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МОРФОЛОГІЧНА ХАРАКТЕРИСТИКА ВЕЛИКИХ БРОНХІВ ЩУРІВ НА ТЛІ ПОСТТРАВМАТИЧНОГО СТРЕСОВОГО РОЗЛАДУ ТА ПІСЛЯ КОРЕКЦІЇ КВЕРЦЕТИНОМ

Війна впливає на повсякденне життя абсолютної більшості українців. Тому нині в Україні посттравматичний стресовий розлад став однією з найактуальніших медико-соціальних проблем. Він характеризується складним патогенезом та коморбідністю з багатьма іншими захворюваннями. Вивчення моделей посттравматичного стресового розладу на щурах, його впливу на різні органи та системи, а також пошук шляхів корекції мають вирішальне значення для відновлення здоров'я постраждалих. У роботі представлені результати морфологічного дослідження впливу посттравматичного стресового розладу на бронхи щура та його корекції кверцетином. Встановлено, що цей розлад викликає суттєві деструктивні зміни у великих бронхах щурів, зокрема, десквамацію епітеліоцитів з утворенням у просвітах бронхів клітинного детриту, гіпергідратацію та лейкоцитарну інфільтрацію слизової оболонки та підслизової основи, розлади гемомікроциркуляції. Внутрішньоочеревинне введення водорозчинного комплексу кверцетину 1 раз за добу протягом 7-ми діб щурам, значно нівелює ураження великих бронхів на тлі постстресового розладу, що свідчить про ефективність цього засобу як стреспротектора.

Ключові слова: посттравматичний стресовий розлад, бронхи, легені, гістологічні зміни, морфологічні зміни, корекція.

The work is a fragment of the research project "Regularities of the morphogenesis of organs, tissues and vascular and nervous formations in normal, pathological and under the influence of exogenous factors", state registration No. 0118U004457.

The Russian invasion of Ukraine has affected the daily life of all segments of the population of our country [10]. Both members of the Armed Forces of Ukraine and civilians are exposed to constant chronic stress. Military personnel experience combat stress as a result of operating in extreme conditions, which is accompanied by potent external and internal stressors. They threaten a person's life, adversely affect their health, reduce performance or lead to disruption. Combat stress can lead to acute psychological reactions and the development of stress disorders [9]. Combat stress is an integral part of the psychological trauma