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Реферати

БІОХІМІЧНІ ОСОБЛИВОСТІ ЗАГОЄННЯ ПІСЛЯОПЕРАЦІЙНИХ РАН ШКІРИ НА ФОНІ ЦУКРОВОГО ДІАБЕТУ У ЩУРІВ ПРИ РІЗНИХ СПОСОБАХ ЗАКРИТТЯ РАН

Лоза Є.О., Марущак М.І., Денефіль О.В., Аветіков Д.С., Кулянда О.О.

Дослідження присвячено вивченню особливостей змін вільнорадикальних процесів у гомогенаті шкіри щурів при різних способах закриття операційних ран, за умов цукрового діабету. Аналіз отриманих результатів дає змогу стверджувати, що застосування шкірного клею достовірно знижує інтенсивність перебігу ВРО у клітинах рубцевозмінених тканин шкіри тварин зі змодельованим цукровим діабетом порівняно із накладанням на рану вузлових швів за аналогічних умов.

Ключові слова: вільнорадикальне окиснення, оксидативний стрес, патологічний рубець.

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БИОХИМИЧЕСКИЕ ОСОБЕННОСТИ ЗАЖИВЛЕНИЕ ПОСЛЕОПЕРАЦИОННЫХ РАН КОЖИ НА ФОНЕ САХАРНОГО ДИАБЕТА У КРЫС ПРИ РАЗЛИЧНЫХ СПОСОБАХ ЗАКРЫТИЯ РАН

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Исследование посвящено изучению особенностей изменений свободнорадикальных процессов в гомогенате кожи крыс при различных способах закрытия операционных ран, при сахарном диабете. Анализ полученных результатов позволяет утверждать, что применение кожного клея достоверно снижает интенсивность течения свободно радикальных процессов в клетках рубцово-измененных тканей кожи животных с смоделированным сахарным диабетом по сравнению с наложением на рану узловых швов при аналогичныхусловиях.

Ключевые слова: свободно радикальное окисление, оксидативныйстресс, патологический рубец.

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THE ROLE OF ARGININE/CITRULLINE CYCLE DISORDERS IN THE PATHOGENESIS OF DOXORUBICIN-INDUCED LIVER INJURY ASSOCIATED WITH NONALCOHOLIC STEATOHEPATITIS IN RATS

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The article presents the results of an experimental study aimed to investigate the features of arginine / citrulline cycle disorders associated with doxorubicin-induced liver injury in rats, concomitant with NASH. The study involved adult fertile □utbr□d □lb□n□r□ts (n=30; m□l□r□ts=15 (50%); f□m□l□r□ts=15 (50%)) w□ght□d 160-220 g. The rats were assigned into 3 groups: Group I (n=10) involved rats with NASH, administered w□th □ntr□□r□t□n□l 5 mg/kg d□□rub□□n f□r 3 d□□s; Gr□u□ II (n=10) □nv□lv□d r□ts w□th□ut N□SH, □dm□n□st□r□d w□th □ntr□□r□t□n□l d□□rub□□n s□m□l□r t□Gr□u□□r□g□m□n; Gr□u□III (n=10) – control group. It has been shown that administration of doxorubicin in rats with NASH leads to disorders of arginine/citrulline cycle, which are characterized by inhibition of arginase activity and activation of citrulline synthesis.

Key words: arginine, citrulline, arginase, doxorubicin, hepatotoxic reactions, nonalcoholic steatohepatitis.

The work is a fragment of the research project "Development of methods for prevention and treatment of the drug-induced internal organs damages", state registration No. 0115U001087.

Doxorubicin, an anthracycline antibiotic, has been extensively used in oncology and oncohematology for over 30 years. Currently, it is considered one of the most effective antitumor drugs with pharmacological feature to accumulate in malignant cells. However, the use of doxorubicin is accompanied by a high risk of side effects due to its high toxicity [3, 8, 10, 13].

From the point of view of studying the toxicity of doxorubicin, certain features of its pharmacokinetics are important, namely the short half-life period lasted for 3-5 minutes, and the long semiejection period, ranging from 24 to 46 hours [12]. Therefore, the development of toxicity and its degree is dependent on the rate of administration of doxorubicin. Upon entry into the blood plasma, doxorubicin, similar to doxorubicinol, binds to blood proteins, penetrates into the cell by passive diffusion and accumulates in tumor cells in concentrations exceeding its extracellular ones by 10-1000 times [12, 15]. The high permeability properties of doxorubicin are due to its lipophilicity, and the preservation of high intracellular concentrations of the drug is due to its DNA-intercalating and binding characteristics [12, 14].

It has been confirmed that DNA is the major target for doxorubicin. The drug accumulates in the cell nucleus with intercalation in the double strand of DNA between base pairs, which leads to inhibition of nucleic acid synthesis. In addition, doxorubicin disrupts the function of nuclear proteins, primarily topoisomerases I, II and helicase, which leads to inhibition of DNA twisting and cell replication [3, 15]. Intercalation of doxorubicin into a DNA molecule inhibits the activity of DNA and RNA polymerases, suspending both DNA replication and RNA transcription. Hence, doxorubicin disrupts the repair of the DNA molecule, which leads to attenuation of cell development in the G1 and G2 phases of the cell cycle and initiation of apoptosis [12].

An important element of the toxicity of doxorubicin, as an antitumor drug, is the impact on both tumor and healthy cells of the body, which multiply rapidly [3, 12, 14, 15]. Moreover, free radicals cause drastic side effects associated with administration of the drug through the mechanisms that provide high antitumor efficacy of doxorubicin [3, 11, 13].

Doxorubicin-induced hepatotoxic reactions can be a significant limiting factor in the overall chemotherapy (CT) in the conventional treatment of cancer patients. Currently, numerous experimental and clinical studies have confirmed the toxic effects of doxorubicin on tissues of the heart, brain, kidneys, liver, pancreas [10, 15]. The probability of development of cytostatic-induced hepatotoxic reactions increases significantly in chronic diffuse hepatic diseases, including non-alcoholic steatohepatitis [5]. Pathogenetically, it is the oxidative stress that is the most studied mechanism of liver damage induced by doxorubicin and other anthracycline antibiotics [13]. Doxorubicin has been confirmed to be associated with an increased risk of hepatotoxic reactions, manifested by elevated blood serum activity of alanine and asparagine aminotransferases, alkaline phosphatase, gamma-glutamyltranspeptidase, bilirubin and its fractions [5]. However, the use of chemotherapeutic drugs, including doxorubicin, affects a number of essential liver functions, namely detoxification and regenerative functions, which can be investigated by determining the content of arginine and ways of its biotransformation.

Arginase is involved in the final stage of the urea cycle, during which arginine is converted to urea and ornithine. Arginase is considered as a marker of hepatotoxicity induced by pharmacological drugs; its altered activity is more sensitive test of liver dysfunction compared to traditional ones. A competitive pathway for the metabolism of L-arginine is the formation of nitric oxide (NO) and citrulline under the influence of NO synthases (NOS). Arginine / citrulline cycle reflects the features of the competitive interaction of arginase and NOS activity [2, 4]. Given the fact that the inducible form of NOS promotes the production of NO as a cytotoxic and anti-inflammatory agent, the study of the balance of arginase and NOS activity may be crucial in studying the pathogenesis of cytostatic-induced liver damage, including the use of doxorubicin.

The purpose of the paper was to study the features of arginine / citrulline cycle disorders associated with doxorubicin-induced liver damage in rats, concomitant with NASH.

Materials and methods. The study involved adult fertile outbred albino rats (n=30; male rats=15 (50%); female rats=15 (50%)) weighted 160-220 g. The study was carried out in two stages. At the first stage 10 rats (5 males and 5 females) were exposed to modeled NASH, induced by a high-calorie diet, containing 42.8% fats (per one animal a day: combination fodder-concentrate granulated 0.04 kg, 72.5% butter 0.01 kg, refined sunflower oil 0.01 kg, palm oil 0.01 kg; 4% aqueous solution of fructose was used as the sole source of liquid) for 9 weeks (from day 1 to day 63). 20 rats received a regular rations of vivarium (per one animal a day: combination fodder-concentrate granulated 0.04 kg, low-fat cheese 0.006 kg, carrots 0.02 kg, cabbage 0.015 kg) for 9 weeks (from day 1 to day 63). Experimental rats were divided into 3 groups:

Group I rats (n=10; males n=5; females n=5) were exposed to modeled NASH, induced by a high-calorie diet from day 1 to day 63, followed by administration of intraperitoneal 5mg/kg doxorubicin for 3 days (from day 64 to day 66) to reach the cumulative doze of 15 mg/kg;

Group II rats (n=10; males n=5; females n=5) were on a regular rations of vivarium from day 1 to day 63, followed by administration of intraperitoneal 5mg/kg/day doxorubicin from day 64 to day 66 to reach the cumulative doze of 15 mg/kg;

Group III rats (n=10; males n=5; females n=5) were on a regular rations of vivarium from day 1 to day 63, followed by administration of intraperitoneal 0.9% sodium chloride solution at a dose of 1 ml for 3 days (from day 64 to day 66).

Decapitation of rats was performed under thiopental anesthesia on day 67 of the observation. The concentration of arginine [6], citrulline [9] and arginase activity [1, 7] were determined in 10% homogenate of rat liver and blood.

The statistical program GraphPad Prism Version 5.00 (GraphPad Software, Inc., San Diego, CA, USA) was used for statistical processing of the resulting data and to carry out parametric and nonparametric statistical analysis. With the normal distribution of data, the results were presented in the form of arithmetic means (M) and their mean accuracy (m). Significance of differences was calculated using Student's t-test. Paired nonparametric methods of Wilcoxon and Mann-Whitney tests were used in the distribution that differs from the normal one. The relationship between the studied values was evaluated using Spearman's correlation analysis. The differences were considered significant when $p < 0.05$.

Results of the study and their discussion. Rats of experimental Group I and II, which were administered with doxorubicin, showed increased concentration of blood arginine by 2.3 and 2 times, respectively, compared to the control group ($p < 0.05$) (table 1). This fact can be explained both by the increased formation of arginine during the activation of protein catabolism, and by the violation of its availability to enzymes involved in biotransformation. Arginine reuptake by cells might be inhibited by ornithine as well as NOS inhibitors [2, 4]. Undoubtedly, the most important in inhibiting arginine metabolism is arginase, which is a regulatory enzyme that determines the predominance of arginine biotransformation pathways for the formation of NO or ornithine as a substrate for the synthesis of putrescine, spermidine and spermine [4].

Table 1

The rates of arginine, citrulline concentration and arginase activity in rat blood with doxorubicin-induced liver damage associated with NASH (M ± m)

Groups	Arginine, mmol/L	Arginase, µmol/mL	Citrulline, µmol/mL
I (n=10)	0.14±0.035*	13.90±1.53*&	423.4±22.40*
II (n=10)	0.12±0.01*	19.18±1.38*	439.4±13.00*
III (n=10)	0.06±0.01	41.24±6.51	627.8±51.72

Note: significant differences: * $p<0.05$ – between the experimental Group I and II and the control group; &-$p<0.05$ – between the values of Group I and II.

In addition, arginase is considered a marker of drug-induced liver damage, which may be more sensitive than generally accepted rates used in routine clinical practice. Apparently, rats of Group I and II, which were administered intraperitoneally with doxorubicin, showed that the activity of blood arginase was by 2.9 and 2.1 time, respectively, lower, compared to Group III ($p < 0.05$) (Table 1). It has been established that in rats of Group I, which were initially exposed to modeled NASH upon reaching cumulative dose of 15 mg/kg doxorubicin, the activity of blood arginase was by 1.4 times lower compared to rats of Group II ($p<0.05$) (table 1). Therefore, it is obvious that NASH leads to more severe doxorubicin-induced liver damage.

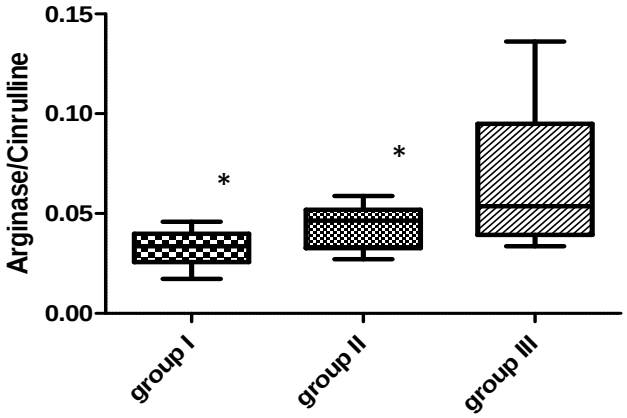

Fig. 1. The arginase / citrulline ratio in blood of rats with doxorubicin-induced liver damage associated with NASH. Note: * $p<0,05$ – significant differences of values in rats of Group I and II compared to the control group.

Citrulline is a by-product of NO in the metabolism of arginine with the involvement of NOS. In rats of Group I and II, blood citrulline concentration was by 1.5 and 1.4 times, respectively, lower, compared to the control group ($p<0.05$) (table 1). The arginase / citrulline ratio in rats of Group I with diet-induced NASH was by 2 times lower, compared to controls (0.03±0.01 vs. 0.06±0.01; $p<0.05$) and by 1.3 times lower compared to rats of Group II (0.03±0.01 vs. 0.04±0.003; $p=0.05$), which were administered with doxorubicin in the intact liver (fig. 1).

In rats of Group II, the arginine / citrulline ratio was by 1.5 times lower compared to controls (0.04±0.003 vs. 0.06±0.01; $p<0.05$). Consequently, the progression of NASH creates the preconditions for the development of doxorubicin-induced liver damage with violation of its detoxification function.

In the liver homogenate of rats of Group I and II, no significant deviations in arginine concentration, compared to the controls, were detected. However, arginase activity in rats of Group I and

II was by 1.6 and 1.7 times, respectively, lower, compared to Group III (p=0.01) (Table 2). Thus, the activity of arginase in the homogenate of liver and blood of experimental animals was reduced in equal proportions regardless of the presence of NASH, which indicates the high toxicity of doxorubicin with the risk for the development of hepatotoxic reactions.

However, in rats of Group I the concentration of citrulline in the liver homogenate was by 1.2 times higher compared with Groups II and III ($p<0.05$) (Table 2). Inverse correlation was found between the concentration of arginine and arginase activity in the liver homogenate of Group I rats ($r =-0.77$; $p<0.05$), as well as a direct correlation between the content of arginine and citrulline ($r=-0.77$; $p<0.05$). This fact may indicate that NASH-related administration of doxorubicin is associated with the activation of the NOS-synthase pathway of arginine metabolism in liver tissue, primarily due to its inducible isoform, which creates an additional factor in hepatocyte damage.

Table 2

The rates of arginine, citrulline concentration and arginase activity in liver homogenate of rats with doxorubicin-induced liver damage associated with NASH (M ± m)

Groups	Arginine, μmol/mL	Arginase, μmol/mL	Citrulline, μmol/mL
I (n=10)	0.31±0.03	1.62±0.23*	68.54±3.37*
II (n=10)	0.29±0.04	1.54±0.12*	57.77±2.41
III (n=10)	0.27±0.02	2.61±0.21	55.67±1.23

Note: *p<0.05 – significant differences between the experimental groups I and II and control Group III (p<0.05).

From this point of view, it is of particular interest to determine the arginase / citrulline ratio in the liver homogenate. Hence, in rats of Group I and II the arginase / citrulline ratio was by 1.9 times (0.025±0.004 vs. 0.047±0.003) and 1.7 times (0.027±0.004 vs. 0.047±0.003), respectively, lower compared to Group III ($p<0.05$) (fig. 2). Therefore, administration of doxorubicin contributes to activation of the NOS-synthase mechanism and inhibition of the arginase pathway of arginine biotransformation in the liver tissues.

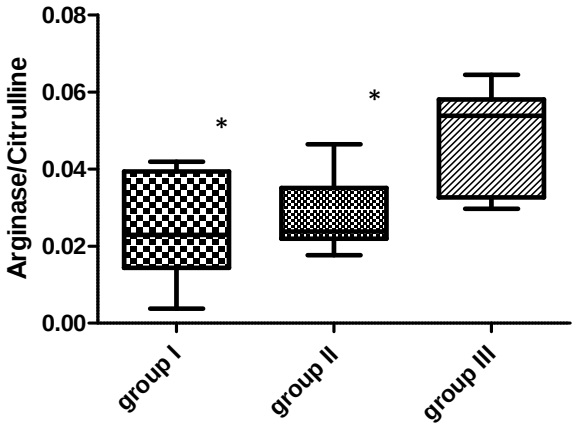

Fig. 2. The arginase / citrulline ratio in liver homogenate of rats with doxorubicin-induced liver damage associated with NASH

Note: * p<0.05 – significant differences of values in rats of Group I and II compared to the control group.

Thus, in the blood of rats administered with doxorubicin intraperitoneally with a cumulative dose of 15 mg / kg, an increase in arginine concentration was detected, which might be associated both with an increase in catabolic processes in the body and impaired reuptake of arginine by cells due to transport system dysfunction.

The meaningful finding of our study is the established inverse dynamics of doxorubicin-induced changes in the concentration of citrulline in the blood and liver tissue. Thus, concentration of blood citrulline was decreased, whereas in the liver homogenate it was increased. Given that citrulline is a by-product of NO in the reaction of arginine biotransformation under the action of NOS [2, 4], we can assume that doxorubicin accumulates in liver tissue, where the NOS pathway of arginine metabolism is activated, which creates a prerequisite for generating aggressive forms of oxygen as a powerful mechanism of pathogenesis of both NASH and doxorubicin-induced liver damage. Reducing the concentration of the blood citrulline may indirectly reduce the synthesis of NO in the endothelium with the formation of endothelial dysfunction as an additional factor in the occurrence of doxorubicin-induced lesions of organs and systems.

Administration of doxorubicin is associated with a decrease in arginase activity in the blood and liver homogenate, accompanied by a decrease in the arginase / citrulline ratio. Importantly, NASH potentiates the disruption of the arginase pathway of arginine biotransformation, leading to impaired detoxification function of the liver. The rate of arginase activity can be used in the clinical practice to evaluate detoxification function of the liver and diagnostics of drug-induced hepatotoxic reactions.

Conclusions

1. Administration of doxorubicin to rats with NASH leads to a decrease in arginase activity in the blood by 2.9 times and in the liver homogenate by 1.6 times, compared with the controls.

2. In the liver homogenate of rats administered with doxorubicin associated with NASH, an increase in the concentration of citrulline by 2 times compared to the control group and rats without NASH, administered with doxorubicin.

3. Decreased arginine / citrulline ratio in the blood and liver tissues of rats administered with doxorubicin indicate activation of the NOS mechanism of arginine metabolism, which is most associated with NASH.

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Реферати

РОЛЬ ПОРУШЕНЬ АРГІНІН/ЦИТРУЛІНОВОГО ЦИКЛУ В ПАТОГЕНЕЗІ ДОКСОРУБІЦИН-ІНДУКОВАНОГО УРАЖЕННЯ ПЕЧІНКИ НА ФОНІ НЕАЛКОГОЛЬНОГО СТЕАТОГЕПАТИТУ У ЩУРІВ

Маслова Г.С., Скрипник Р.І., Гопко О.Ф., Скрипник І.М.

У статті представлені результати експериментального дослідження метою якого було дослідити особливості порушень аргінін/цитрулінового циклу на фоні доксорубіцин-індукованого ураження печінки у щурів із урахуванням супутнього неалкогольного стеатогепатиту (НАСГ). Дослідження проведені на 30 білих нелінійних статевозрілих щурах, із них 15 (50%) самців, 15 (50%) – самок вагою 160-220 г. Щури були розподілені на 3 групи: I (n=10) – щури із НАСГ, яким впродовж 3-х днів внутрішньочеревно вводили доксорубіцин із розрахунку 5 мг/кг/добу; II (n=10) – щури без НАСГ, яким вводили доксорубіцин аналогічно I групі; III (n=10) – група контролю. Показано, що ведення доксорубіцину на фоні НАСГ призводить до порушень у циклі аргінін/цитрулін, які характеризуються пригніченням активності аргінази та активацією синтезу цитруліну.

Ключові слова: аргінін, цитрулін, аргіназа, доксорубіцин, гепатотоксичні реакції, неалкогольний стеатогепатит.

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РОЛЬ НАРУШЕНИЙ АРГИНИН/ЦИТРУЛИНОВОГО ЦИКЛА В ПАТОГЕНЕЗЕ ДОКСОРУБИЦИН-ИНДУЦИРОВАННОГО ПОВРЕЖДЕНИЯ ПЕЧЕНИ НА ФОНЕ НЕАЛКОГОЛЬНОГО СТЕАТОГЕПАТИТА У КРЫС

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В статье представлены результаты экспериментального исследования, целью которого исследовать особенности нарушений аргинин/цитруллинового цикла на фоне доксорубицин-индуцированного поражения печени у крыс с учетом сопутствующего неалкогольного стеатогепатита (НАСГ). Исследования проведены на 30 белых нелинейных половозрелых крысах, из них 15 (50%) самцов, 15 (50%) – самок, весом 160-220 г. Крысы были разделены на 3 группы: I (n=10) – крысы с НАСГ, которым в течение 3-х дней внутрибрюшинно вводили доксорубицин из расчета 5 мг/кг/сутки; II (n=10) – крысы без НАСГ, которым вводили доксорубицин аналогично I группе; III (n=10) – группа контроля. Показано, что введение доксорубицина на фоне НАСГ приводит к нарушениям в цикле аргинин/цитруллин, которые характеризуются угнетением активности аргиназы и активацией синтеза цитруллина.

Ключевые слова: аргинин, цитруллин, аргиназа, доксорубицин, гепатотоксические реакции, неалкогольный стеатогепатит.

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