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PATHOGENETIC IMPORTANCE OF INTRAMITOCHONDRIAL OXIDATIVE MECHANISM IN CONDITIONS OF EXPERIMENTAL ACUTE PYELONEPHRITIS COMPLICATED BY HYPERGLYCEMIA

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The purpose of the study was to determine the oxidative stress pathogenetic role in the kidney mitochondria energy metabolism disorders progress in conditions of acute experimental pyelonephritis complicated by hyperglycaemia and study of the drug impact in these metabolic disorders. Acute pyelonephritis alone and being complicated by a hyperglycemic state reproducing diabetes mellitus I and II types were modeled in rats. Rats with acute pyelonephritis complicated by diabetes mellitus I and II type received both etiotropic drug influence and etiopathogenetic drug influence for 14 days. The activity of prooxidant (NADPH-oxidase and xanthineoxidase) and mitochondrial enzymes cytochromeoxidase and adenosinetriphosphatase were studied in kidneys of rats 28 days after the trial start. The comorbid hyperglycemic state on the background of acute pyelonephritis contributes to rats' kidneys metabolic disorders progress associated with oxidative stress further development against the background of mitochondria energy metabolism disorders. The use of etiopathogenetic drug influence, in contrast to etiotropic drug influence, has a positive impact on prooxidant enzymes activities cytochromeoxidase and adenosinetriphosphatase in kidneys of rats with acute pyelonephritis complicated by diabetes mellitus I and II type. A pathogenetically important link in acute pyelonephritis complicated manifestation is the presence of a concomitant hyperglycemic state with the development of mitochondrial dysfunction in kidney cells and oxidative stress. The data of the study is an experimental background of etiopathogenetic drug influence reasonability in complex therapy of patients with acute pyelonephritis with concomitant diabetes mellitus.

Key words: oxidative stress, energy metabolism, mitochondria, acute pyelonephritis, hyperglycemia, enzymes, drug effect.

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ПАТОГЕНЕТИЧНА ЗНАЧУЩІСТЬ ВНУТРІШНЬОМІТОХОНДРІАЛЬНОГО ОКСИДАТИВНОГО МЕХАНІЗМУ ЗА УМОВ ЕКСПЕРИМЕНТАЛЬНОГО ГОСТРОГО ПІЄЛОНЕФРИТУ, УСКЛАДНЕНОГО ГІПЕРГЛІКЕМІЄЮ

Метою дослідження було визначення патогенетичної ролі оксидативного стресу у розвитку порушень енергетичного обміну в мітохондріях нирок за умови гострого пієлонефриту, ускладненого гіперглікемією та вивчення медикаментозного впливу на ці метаболічні порушення. У щурів моделювали гострий пієлонефрит та гострий пієлонефрит, ускладнений гіперглікемічним станом при цукровому діабеті I та II типу. Щури з гострим пієлонефритом, ускладненим цукровим діабетом I та II типу, протягом 14 днів отримували етіотропний медикаментозний вплив та етіопатогенетичний медикаментозний вплив. Через 28 діб після початку моделювання в нирках щурів досліджували активність прооксидантних (НАДФН-оксидаза та ксантиноксидаза) та мітохондріальних (цитохромоксидаза та аденозинтрифосфатаза) ферментів. Супутній гіперглікемічний стан на тлі гострого пієлонефриту сприяє поглибленню метаболічних порушень в нирках щурів, пов'язаних з подальшим розвитком оксидативного стресу на тлі порушень енергетичного обміну в мітохондріях. Застосування етіопатогенетичного медикаментозного впливу, на відміну від етіотропного медикаментозного впливу, позитивно впливає на активність прооксидантних ферментів цитохромоксидази та аденозинтрифосфатази в тканині нирок у щурів при гострому пієлонефриті, ускладненому цукровим діабетом I та II типу. Патогенетично важливою ланкою ускладненого перебігу гострого пієлонефриту є наявність супутнього гіперглікемічного стану з порушенням енергетичного обміну в мітохондріях нирок та оксидативного стресу. Отримано експериментальне обґрунтування доцільності застосування етіопатогенетичного медикаментозного впливу в комплексній терапії хворих з гострим пієлонефритом при супутньому цукровому діабеті.

Ключові слова: оксидативний стрес, енергетичний обмін, мітохондрії, гострий пієлонефрит, гіперглікемія, ферменти, медикаментозний вплив.

The study is a fragment of the research project "The role of cellular and tissue metabolism in the diagnosis, clinical manifestation and treatment of kidneys, urinary tract and genital organs diseases", state registration No. 0121U108881.

The medical and social significance of acute pyelonephritis (AP) with diabetes mellitus (DM) comorbidity is determined by this common pathology frequency of occurrence progressive increase together with the development of working age persons disabling and quality-of-life declining systemic which include nephro-, retino- and neuropathy [7]. Hyperglycemia, triggering a complex of pathological reactions, including non-enzymatic glycosylation, oxidative stress, inflammatory and profibrotic changes, considered to be a key link in their occurrence and progression [1, 12, 14]. The oxidative stress is one of the kidney damage triggering mechanisms in the course of inflammatory diseases, including AP and

concomitant DM through both oxygen reactive compounds and peroxidation products (i.e., superoxide, hydrogen peroxide, hydroxyl radical, singlet oxygen, methylglyoxal, malonic dialdehyde, etc.) level increase. Mitochondrial function disturbance we suppose has definite importance in the abovementioned compounds production [1, 4].

Hyperglycemia is well known to have a key pathogenetic importance in oxygen reactive compounds excessive formation in kidneys. The initial stage of hyperglycemia pathogenic influence on kidneys characterizes by glomerular both hyperfiltration and hypertrophy together with glomerular endothelial cells injure which dysfunction has not yet been sufficiently studied [9].

We believe important is that the mitochondrial dysfunction develops due to prooxidaive-antioxidative equilibrium impairment in conditions of AP comorbid pathology with DM thus might has pathogenetic importance in the course of kidney inflammatory diseases [6, 9]. Fundamentally important to develop methods of the studied comorbid pathology pathogenetically determined pharmacological correction using drugs that have metabolic correcting activity, nephrocytoprotective and antioxidant action [1, 6, 13]. Current work is devoted to our supposition verification as well as to determination of the AP complicated by DM pharmacological correction efficacy.

The purpose of the study was to determine the oxidative stress pathogenetic role in the kidney mitochondria energy metabolism disorders progress in conditions of acute experimental pyelonephritis complicated by hyperglycaemia. The additional purpose of the work was to study the kidney mitochondria metabolic disorders pharmacological correction efficacy.

Materials and methods. Experimental trials were performed in conditions of the chronic experiment using 110 Wistar rats, weighing 200–300 g, aged 8–9 months, according to "General ethical principles of animal experiments" approved by the 5th National Congress of Bioethics (Kyiv, 2013) and statements of "European convention for the vertebrate animals' protection used with experimental and other purposes" (Strasbourg, 1986). The animals received water and food *ad libitum* throughout the whole trial.

The animals were randomized as follows: group 1 – intact rats (n=15); group 2 – animals with AP (n=14); group 3 – animals with AP complicated by DM I type (n=12); group 4 – animals with AP complicated by DM II type (n=13); group 5 – animals with AP complicated by DM I type received etiotropic drug influence (EDI, n=13); group 6 – animals with AP complicated by DM II type received EDI (n=14); group 7 – animals with AP complicated by DM I type received etiopathogenetic drug influence (EPDI, n=14); group 8 – animals with AP complicated by DM II type received EPDI (n=15).

Type I DM was reproduced by streptozotocin (55 mg/kg; "Serva", Germany) single intraperitoneal (i.p.) injection which was dissolved in 10 mM citrate buffer (pH=4.5). Type DM was reproduced by streptozotocin (35 mg/kg) double i.v. administration. Animals received high-calorie fatty food in case of type II DM modelling. To prevent lethality and reduce weight while hyperglycemia keeping animals were injected with insulin (2 IU) at a blood glucose level above 25 mmol/l. The animals with persistent hyperglycaemia were selected for the trials. Hyperglycaemia level was determined by glucose content measuring in the blood obtained from the rats' tail vein using an indicator test strip ("One Touch", Germany; the error of the method equal to ±1 %).

The AP in rats with verified DM was modelled by a single rectal Escherichia coli isolate (bacteriuria level of 107 Colony-Forming Unit in 1 ml) administration obtained from the urine of a patient with AP. The animals were subjected to cold stress on the 2nd day of the trial for 2 hrs at a temperature in the range of 0 – +2°C. The experimental AP is relevant to AP clinical manifestation confirmed by an expressed bacteriuria, leukocyturia and rats peripheral blood leukocyte's formula violation.

Rats were administered EDI and EPDI on the 4th day after AP induction during the 14 days of the trial. EDI means that rats with DM I and II types on the AP background were intramuscularly (i/m) administered the antibiotic "Hepacef" (60 mg/kg; "Kievmedpreparat", Ukraine). EPDI means that rats with DM I and II types on the AP background additionally to "Hepacef" were *per os* administered by "Nukleks" (ribonucleic acid; 21 mg/kg; "Valartin Pharma", Ukraine) and i.m. administered by "Armadin" (2-ethyl-6-hydroxypyridine-succinate; 4.5 mg/kg; "Microchem", Ukraine).

In rats after euthanasia with i.p. sodium thiopental overdose (50 mg/kg) on the 28th day of the trials, the kidneys were removed, their homogenate was prepared in a 9-fold volume of 0.32 mol of sucrose per 0.05 mol of Tris buffer (pH=7.36) in a homogenizer with Teflon surfaces and subjected to differential

centrifugation in a refrigerated centrifuge RS-6. Nuclei were precipitated at 1000g for 10 min., then mitochondria at 12000g for 20 min. For biochemical studies, the supernatant was used to determine both the NADPH-oxidase and xanthineoxidase (XO) activities spectrophotometrically. The cytochromeoxidase (CCO) and adenosinetriphosphatase (ATP) activities were determined in mitochondria.

The results obtained were statistically calculated using the parametric ANOVA test, followed by the Newman-Kulls test, as a measure of compliance. The minimal statistical probability was determined at $p<0.05$.

Results of the study and their discussion. A significant increase of NADPH-oxidase activity by 39.6 % and a less pronounced XO activation by 28.9 % vs the normal values was established in the kidneys of animals with AP (Table 1).

Table 1

NADPH-oxidase and xanthineoxidase activities in kidneys of rats with acute pyelonephritis with comorbid diabetes mellitus and under the drugs impact

Studied parameters	The conditions of the trial				
	Intact rats	Acute pyelonephritis	Acute pyelonephritis + diabetes mellitus		
			Without drug influence	EDI	EPDI
Acute pyelonephritis + diabetes mellitus type I					
NADPH-oxidase, ncat/g	98.6±7.1	137.6±9.1 **	209.1±15.6 *** ##	184.7±14.4 *** #	144.7±12.4 ** @ *f*
Xanthineoxidase, ncat/g	43.6±3.6	56.2±4.2 *	78.5±6.3 *** ##	69.6±4.7 *** #	54.6±3.8 * @ *f*
Acute pyelonephritis + diabetes mellitus type II					
NADPH-oxidase, ncat/g	98.6±7.1	137.6±9.1 **	191.6±14.1 *** #	163.4±12.8 ***	123.5±8.8 * @@@ *f*
Xanthineoxidase, ncat/g	43.6±3.6	56.2±4.2 *	74.5±5.3 *** #	62.0±4.8 **	47.5±3.2 @@@ *f*

Notes: * – $p<0.05$, ** – $p<0.01$ and *** – $p<0.001$ – significant differences of the studied indices compared to analogous control indexes; # – $p<0.05$ and ## – $p<0.01$ – significant differences of the studied indexes compared to analogous indices in rats with AP; @ – $p<0.05$ and @@@ – $p<0.001$ – significant differences of the studied indices compared to analogous indexes in rats with AP + DM without drug influence; *f* – $p<0.05$ – significant differences of the studied indexes compared to analogous indices in rats with AP + DM with EDI (ANOVA + Newmann-Keuls statistic criteria were used in all calculations).

Cytochromeoxidase activity in the kidneys of rats with AP decreased by 23.4 % ($p<0.05$), ATP activity decreased by 21.7 % ($p<0.01$) pertaining to the same indexes in intact rats (Table 2).

Table 2

Mitochondrial cytochromeoxidase and adenosinetriphosphatase activities in kidneys of rats with acute pyelonephritis with comorbid diabetes mellitus and under the drugs impact

Studied parameters	The conditions of the trial				
	Intact rats	Acute pyelonephritis	Acute pyelonephritis + diabetes mellitus		
			Without drug influence	EDI	EPDI
Acute pyelonephritis + diabetes mellitus type I					
Cytochromeoxidase, ncat/g	218.4±16.8	167.3±14.0*	120.8±9.4*** #	132.3±8.7***	162.0±10.3* @@ *f*
Adenosinetriphos-phatase, ncat/g	26.5±1.3	20.8±1.1**	15.1±1.1*** #	16.4±1.2*** #	19.8±1.1*** @@ *f*
Acute pyelonephritis + diabetes mellitus type II					
Cytochromeoxidase, ncat/g	218.4±16.8	167.3±14.0*	130.9±10.3*** #	147.0±10.8**	182.7±13.1@@ *f*
Adenosinetriphos-phatase, ncat/g	26.5±1.3	20.8±1.1**	16.5±1.0*** #	18.3±1.3***	22.5±1.5* @@ *f*

Notes: * – $p<0.05$, ** – $p<0.01$ and *** – $p<0.001$ – significant differences of the studied indexes compared to analogous control indexes; # – $p<0.05$ – significant differences of the studied indexes compared to analogous indexes in rats with AP; @@ – $p<0.01$ – significant differences of the studied indexes compared to analogous indexes in rats with AP + DM without drug influence; *f* – $p<0.05$ – significant differences of the studied indexes compared to analogous indexes in rats with AP + DM with EDI (ANOVA + Newmann-Keuls statistic criteria were used in all calculations).

Comorbid DM significantly worsened metabolic state in kidneys of rats with AP that was followed by active oxygen species production increase.

Both NADPH-oxidase and XO activities in rat's kidneys in conditions of AP with DM I type without drug influence (DI) increased by 51.9 % and by 39.8 %, correspondently, if compared with the

same indexes in rats with AP ($p<0.01$). The investigated parameters continued to different vs the same control indexes ($p<0.001$).

The analogous decrease of enzymatic activities we registered while study both CO and ATP activities in kidneys of rats with AP with DM I type without DI ($p<0.05$).

NADPH-oxidase and XO activities in kidneys of rats with AP and comorbid DM II type without DI increased by 39.2 % and 94.3 %, correspondently, compared to the same indices in rats with AP ($p<0.05$). These indices continued to different vs the same control indices ($p<0.001$).

Similar pattern of enzymatic activities change we observed while study both CO and ATP activities in kidneys of rats with AP with DM II type without DI ($p<0.05$).

Administration of EDI to rats with AP comorbid with DM failed to receive the significant changes of the investigated enzymes activity ($p>0.05$).

The use of EPDI in rats with AP comorbid with DM type I caused a significant decrease in both NADPH-oxidase and XO activities in the kidneys by 21.7 % and 21.6 %, correspondently, pertaining the same indices in the same animals which were administered EDI ($p<0.05$). These data were by 30.8 % and 30.5 % less compared to the same indices in the same rats without the DI ($p<0.05$). One should stress that data obtained exceeded the control values by 46.7 % ($p<0.01$) and by 25.3 % ($p<0.05$), respectively.

We receive a positive EPDI impact on mitochondrial enzymes CO and ATP activities in animals with AP and concomitant type I DM characterized by their activities significant increase pertaining the same data in the same rats with ADI administration ($p<0.05$). The data received in these rats exceeded significantly the same data in rats with AP comorbid with DM I type without the DI ($p<0.05$) and were less if compared to the control values ($p<0.05$).

Both NADPH-oxidase and XO activities in rats with AP comorbid with DM II type were decreased by 24.4 % and 23.4 % vs the same indices in the same rats that were administered by EDI ($p<0.05$). These data were also less comparing the same indices in the same rats that did not received DI ($p<0.001$).

EPDI administration to rats with AP and concomitant DM II type resulted in both CO and ATP activities increase comparing with the same indices in the same rats that were administered by EDI ($p<0.05$) and in the same rats that were not received any DI ($p<0.01$).

Thus, while determining the influence of DM on kidneys metabolic state in rats with AP, we obtained data indicating an AP manifestation significant complication against the of hyperglycaemia background which is associated with reactive oxygen species production increase. Our investigation of enzymatic activities in rats with AP indicate oxidant enzymes NADPH-oxidase and XO activation together with mitochondrial enzymes CO and CO activities suppression We also set up the further increase of mitochondrial enzymes NADPH-oxidase and XO in conditions of AP comorbidity with DM, especially of the type I that make a considerable impact into kidneys' mitochondrial dysfunction progress.

The revealed kidneys' metabolic disorders prove both the oxidative stress and mitochondrial dysfunction significant pathogenetic importance in case of kidneys pathological changes in experimental conditions of AP with the accompanying DM.

These conclusions obtained on the basis of the significant amount of data analysis are confirmed by more effective etiopathogenetic correction of the studied kidneys comorbid state against the hyperglycemia background which characterized by all studied antioxidant and mitochondrial enzymes activities normalization. In terms of data obtained discussion we want to note the following which will allow us to understand better the oxidative processes place and role in kidney damage against the background of diabetes pathogenesis.

NADPH-oxidase isozymes are known to perform an important function in normal conditions to regulate apoptosis and fibrosis, cell growth and differentiation due to reactive oxygen species generation [10]. From the other side, NADPH-oxidase and XO dysregulation as well as their hyperactivation can contribute to various pathological conditions development and aggravation, including diabetic kidney damage. This is due to the fact that hyperglycaemia activates NADPH-oxidase and XO, thus increasing free radical compound levels that, in turn, result in the development of oxidative changes in kidney tissues. One should stress that oxidant enzyme activities' unnecessary activation regulatory influence can serve as an important therapeutic strategy for these pathological disorders' treatment [5, 10].

ATP activation in the kidney tissues of animals is known during the course of DM [11] which might be related to the time of hyperglycemia development and glomerular filtration rate hurt. Thus, Na^+-

K^+-ATPase, the largest ATP consumer, is located on tubular cells basolateral membrane and reduces intracellular Na^+ concentration and ensures Na^+ absorption through the apical membrane [6, 7]. Na^+-K^+-ATPase activity is reported to be decreased in the erythrocytes of patients with DM type II, especially in diabetic neuropathy [3]. DM-induced ischemia, in turn, causes kidney tissue metabolic disorders development including an ATPase activity decrease, which can be the basis of ATP deficiency with nephrocytes subsequent damage [1, 7].

Oxidative stress and prolonged inflammation of, especially, the urinary tract is considered the main factors of both mitochondrial dysfunction and diabetic complications development. The relation between ATPase activity decreases and tubulointerstitial lesions exacerbation with kidney fibrosis was shown earlier [15]. An acute and chronic Na^+-K^+-ATPase activity decrease occurs in various pathological conditions including kidney diseases [15]. Logically to suppose that mitochondrial dysfunction in diabetes affects the bioenergetic processes (electron transport and ATP generation) in kidneys' glomerular and tubular cells and contributes to pathological changes' progression [6].

Therefore, the comorbid pathological conditions using the concomitant DM in our case affects the inflammatory and infectious processes in urinary tract and kidneys manifestation, which exacerbation is caused by oxidative and carbonyl stress development against the background of antioxidant enzymatic system activity collapse.

We emphasize that in this study we receive exact data regarding the possibility of correcting with the specified drugs both mitochondrial dysfunction on the example of the studied energy metabolism enzymes ATP and CO and oxidant enzymes activity on the example of NADPH-oxidase and XO in rats kidneys with a complicated AP manifestation with the accompanying hyperglycemia.

These data are somewhat consistent with the results of pathogenetic pharmacological correction efficacy using energetic supply restore by hormonal drugs [2, 8]. It was shown that use of energetic drug which includes ribonucleic acid and free-radical processes inhibitor with a membrane-protective effect, 2-ethyl-6-methyl-3-hydroxypyridine-succinate, provided positive impact on intoxication integral index and on the oxidant-antioxidant ratio in kidneys of animals with AP comorbid with DM.

Summarizing, we believe that data obtained are in favour of kidney mitochondrial dysfunction in the presence of concomitant hyperglycemic state and oxidative stress serve as the pathogenetically important link in case of AP complicated manifestation. The data of the study is an experimental background of EPDI reasonability in complex therapy of patients with AP with concomitant DM. Therefore, the new pathogenetically oriented methods of treatment creation, taking into account acute pyelonephritis comorbid with hyperglycemia molecular mechanisms of pathogenesis, using the potential of antioxidant therapy and other pharmacological agents aimed to kidney disease treatment and prevention of progression is a promising and relevant direction of fundamental and clinical studies today.

Conclusions

1. A significant increase in NADPH-oxidase and XO activities against the background of ATP and CO activities decrease in rat's kidneys with AP indicates the oxidative stress and mitochondrial dysfunction development.

2. Concomitant DM, especially of type I, against the background of AP without DI contributes to kidneys metabolic disorders progress associated with the further development of oxidative stress against the background of mitochondrial dysfunction: in AP comorbid with DM type I diabetes, NADPH-oxidase activity increased by 51.9 %, XO – by 39.8 %, CO activity decreased by 27.7 % and ATP – by 27.5 %; in AP comorbid with DM type II diabetes, NADPH-oxidase and XO activities increased by 39.2 % and 32.6 %, respectively, CO and ATP activities decreased by 21.8 % and 20.5 %, respectively.

3. The use of EPDI has a positive impact on oxidant enzymes and mitochondrial CO activities in rats' kidney with AP and comorbid DM type I (decrease in NADPH-oxidase activity by 21.7 %, XO – by 21.6 % and CO activity increase by 22.4 %, ATP – by 20.8 %) and DM type II (decrease in NADPH-oxidase activity by 24.4 %, XO – by 23.4 % and CO activity increase by 24.3 %, ATP – by 22.8 %).

4. Kidney mitochondrial dysfunction in the presence of concomitant hyperglycemic state and oxidative stress serve as the pathogenetically important link in case of AP complicated manifestation. The

data of the study is an experimental background of EPDI reasonability in complex therapy of patients with AP with concomitant DM.

Prospects for further research aimed to create the new pathogenetically oriented methods of treatment, taking into account acute pyelonephritis comorbidity with hyperglycemia molecular mechanisms of pathogenesis, using the potential of antioxidant therapy and other pharmacological agents aimed to kidney disease treatment and prevention of progression.

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