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S.O. Borisov, F.I. Kostev, O.V. Borisov, I.M. Mikheytseva[1], S.G. Kolomiichuk, M.V. Shostak, O.I. Tiron
Odesa National Medical University, [1]SI "The Filatov Institute of Eye Diseases and Tissue Therapy of National Academy of Medical Sciences of Ukraine", Odesa

INTRARENAL ENERGY METABOLISM CHANGES IN CONDITIONS ACUTE EXPERIMENTAL PYELONEPHRITIS COMPLICATED BY HYPERGLYCEMIA WITH PHARMACOLOGICAL CORRECTION

e-mail: borisov-urol@ukr.net

The purpose of the study was to establish the role of energetic metabolism indexes in the pathogenesis of acute pyelonephritis with concomitant diabetes mellitus in an experimental condition with pharmacological correction. 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 types received both etiotropic drug influence and etiopathogenetic drug influence for 14 days. The content of lactate, pyruvate, glucose-6-phosphate, ATP, and ADP, together with the NAD/NADH ratio, were studied in the kidneys of rats 28 days after the trial started. The comorbid hyperglycemic state on the background of acute pyelonephritis contributes to rats' kidney energy disorders' progress manifested by lactate level increase and pyruvate, glucose-6-phosphate, and ATP levels decrease. Further progression of energy metabolism disorders was found in the kidneys of rats with acute pyelonephritis with concomitant diabetes mellitus, especially of the I type. Such energetic chaos manifested in the form of ATP reserves depletion, which may be associated with ATP-impaired synthesis that intensifies hyperglycemia and contributes to both intrarenal hypoxia and acidosis development. Succinate-containing compounds and a ribonucleic acid donor combined administration cause a restorative impact on energy metabolism indexes in kidney tissue in acute pyelonephritis complicated by diabetes mellitus. The results of the study indicated the reasonability of succinate-containing compounds and ribonucleic acid donors' co-administration in clinical conditions to normalize lactate, pyruvate, and energy potential content in patients with acute pyelonephritis with concomitant diabetic kidney damage.

Key words: acute pyelonephritis, streptozotocin-induced diabetes, rats, energy metabolism, drug correction.

С.О. Борисов, Ф.І. Костєв, О.В. Борисов, І.М. Михейцева, С.Г. Коломійчук, М.В. Шостак, О.І. Тірон

ЗМІНИ ВНУТРІШНЬОНИРКОВОГО ЕНЕРГЕТИЧНОГО ОБМІНУ ПРИ ГОСТРОМУ ЕКСПЕРИМЕНТАЛЬНОМУ ПІЄЛОНЕФРИТІ, УСКЛАДНЕНОМУ СУПУТНЬОЮ ГІПЕРГЛІКЕМІЄЮ, ПРИ ФАРМАКОЛОГІЧНІЙ КОРЕКЦІЇ

Метою дослідження було визначення ролі показників енергетичного обміну в патогенезі гострого пієлонефриту при супутньому цукровому діабеті в експерименті за умов фармакологічної корекції. 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 визначали вміст лактату, піруват, глюкозо-6-фосфату, АТФ та АДФ, а також співвідношення вільних НАД/НАДН. Супутній гіперглікемічний стан на тлі гострого пієлонефриту сприяє поглибленню енергетичних порушень в нирках щурів, які проявляються зростанням рівня лактату та зниженням піруват, глюкозо-6-фосфату, АТФ. У тканинах нирки при гострому пієлонефриті на тлі супутнього цукрового діабету, особливо при I типі, виявлено подальше поглиблення порушення енергетичного обміну, виснаження резерву АТФ, що може бути пов'язано з порушенням синтезу АТФ, поглиблюючи стан гіперглікемії та сприяючи розвитку гіпоксії та ацидозу. Сумісне введення сукцинат-вмісних сполук і донатора рибонуклеїнової кислоти спричинило відновлюючий вплив на показники енергетичного обміну в тканині нирок при гострому пієлонефриті, ускладненому цукровим діабетом. Результати дослідження свідчать про доцільність сумісного введення сукцинат-вмісних сполук і донаторів рибонуклеїнової кислоти в клінічних умовах з метою нормалізації вмісту лактату, піруват та енергетичного потенціалу в організмі хворих на гострий пієлонефрит з супутнім діабетичним ураженням нирок.

Ключові слова: гострий пієлонефрит, стрептозотоцин-спричинений діабет, щури, енергетичний обмін, медикаментозна корекція.

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Intrarenal metabolic and functional process disorders are detected in patients with acute pyelonephritis (AP) [8]. Their indexes might have diagnostic value in case of kidney dysfunction in patients with AP [1]. Diabetes mellitus (DM) is characterized by functional lesions and significant disturbances of carbohydrate and energy metabolism inside different internal organs, including the kidneys [2].

Thus, one could register kidney acid-excretory function changes in rats of an adaptive nature throughout the experimental DM dynamics.

At the same time, the overloading of intrarenal mechanisms of acid secretion leads to proximal and distal mechanisms of urine acidification failure and kidneys compensatory abilities in acid-base balance regulation. As a result, the tubular influx of sodium and potassium ions disorders and their redistribution chaos between the vascular, tubular, and interstitial renal compartments leads to local hemodynamics inside kidneys disturbance, interstitium changes both in hydrophilicity and osmolarity as well as the mechanisms of urine concentration and water-osmotic balance regulation damage [2, 3].

Renal complications development in conditions of DM is associated with metabolic process intensification induced by prolonged hyperglycemia and hypoxia [9]. These conditions additionally may be interconnected, i.e., cellular hypoxia caused by hyperglycemia, from one side, and mitochondrial reactive oxygen species generation, from the other, might contribute to further hyperglycemic damage of an organism [9]. This induces the carbohydrate oxidation aerobic phase inside tissues suppression, glycolytic processes intensification, and energetic balance efficiency reduction [14].

Our attention is attracted to intrarenal metabolic changes analysis in rats with AP and concomitant DM, considering the possibility of hypoxic state development, both morphological and functional complications formation, which can lead to diabetic nephropathy progress [7].

The importance of the topic chosen for the study is highlighted by the proven fact that urinary tract recurrent infection is a higher risk in patients with II type DM [7]. These patients demonstrated the expressed renal dysfunction against the background of a significant increase in glycosylated hemoglobin levels, which did not improve despite intensive treatment. Uncontrolled glycemia, in turn, increases the risk of recurrent urinary tract infection, i.e., causes pathological mechanisms to autoactivate this pathological process.

Therefore, identifying risk factors, including intrarenal and whole organism metabolism detection in conditions of urinary tract infection against the background of hyperglycemia, will contribute to developing both a strategy for disease recurrence prevention and drug selection.

Taking into account the energy metabolism's principal importance in cellular homeostasis maintenance as well as its disorders role in kidney inflammatory diseases, especially against the background of hyperglycemia, we supposed it suitable to investigate the principal possibility of energetic dysfunction pharmacological correction in experimental conditions of these two mutually aggravating pathological processes using drugs with energotropic and antioxidant effects.

The purpose of the study was to establish the role of energetic metabolism indexes in the pathogenesis of acute pyelonephritis with concomitant diabetes mellitus in an experimental condition with pharmacological correction.

Materials and methods. Experimental trials were performed in conditions of the chronic experiment using 122 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 protection of vertebrate animals used for 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 induced by a single intraperitoneal (i.p.) injection of streptozotocin (55 mg/kg; "Serva", Germany) which was dissolved in 10 mM citrate buffer (pH=4.5). Type II DM was reproduced by double i.v. streptozotocin (35 mg/kg) administration. Animals received high-calorie fatty food in the case of type II DM modelling which allowed them to simulate a condition as close as possible to type II DM manifested by moderate and stable hyperglycemia.

To prevent lethality and reduce weight while hyperglycemia, animals were injected with insulin (2 IU; "Farmak", Ukraine) 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 rat's tail vein using an indicator test strip ("One Touch", Germany; the method error equal to ±1 %). A glucose tolerance test was performed to confirm diabetes presence in rats.

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 a change in the formula of the rats' peripheral blood leukocytes.

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 by 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).

Kidneys were removed in rats after euthanasia using i.p. sodium thiopental overdose (50 mg/kg) on the 28th day of the trials. All subsequent operations were performed in the cold (0±4°C).

For biochemical studies, the supernatant was obtained after kidneys homogenate centrifugation in which lactate, pyruvate, glucose-6-phosphate (GP), ATP, and ADP content were detected according to generally accepted methods using "Specol-210" (Germany) spectrophotometer.

Free NAD/NADH ratio was calculated using the formula:

$NAD/NADH = 1/K_{LDG} \bullet ([pyruvate]/[\ lactate]$,

in which $K^{-1} = 1.11 \bullet 10^{-4}$ – equilibrium constant of the lactatedehydrogenase reaction.

The data obtained were expressed as mean±standard error of the mean in μmol/g of tissue. The draw data were statistically calculated using the parametric ANOVA test and the post-hoc Newman-Keulls test. Kruscall-Wallis nonparametric test was used for absolute data and ratio statistical analysis. The minimal statistical probability was determined at $p<0.05$.

Results of the study and their discussion. The investigation of lactate and pyruvate levels in animals with experimental AP and concomitant type I DM revealed significant changes in these substances' levels in rats' kidneys (Table 1).

Table 1

Lactate and pyruvate content and free NAD/NADH ratio in kidneys of rats with acute pyelonephritis with comorbid diabetes mellitus under the drug's influence

Investigated 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				
Lactate, μmol/g	1.18±0.06	1.62±0.11 **	2.24±0.16 ***††	2.03±0.14 ***†	1.53±0.12 *‡#
Piruvate, μmol/g	0.123±0.007	0.102±0.006 *	0.079±0.007 ***†	0.088±0.005 ***	0.105±0.006 ‡‡#
Lactate/ piruvate	9.59	15.88	28.35	23.10	14.57@
NAD/NADH	936.94	567.57	315.32	387.39	621.62
	Acute pyelonephritis + diabetes mellitus type II				
Lactate, μmol/g	1.18±0.06	1.62±0.11***	1.98±0.12***†	1.78±0.12***	1.39±0.08*‡‡‡#
Piruvate, μmol/g	0.123±0.007	0.102±0.006*	0.084±0.006***†	0.092±0.005**	0.112±0.007‡‡#
Lactate/ piruvate	9.59	15.88	23.57	19.35	12.41@
NAD/NADH	936.94	567.57	378.38	468.47	729.73

Notes: * – $p<0.05$, ** – $p<0.01$ and *** – $p<0.001$ – significant differences of the studied indexes compared to analogous control indexes; † – $p<0.05$ and †† – $p<0.01$ – significant differences of the studied indexes compared to analogous indexes in rats with AP; ‡ – $p<0.05$, ‡‡ – $p<0.001$ and ‡‡‡ – $p<0.001$ – significant differences of the studied indexes compared to analogous indexes in rats with AP + DM without drug influence; # – $p<0.05$ – 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); @ – $p<0.05$ – significant differences of the studied indexes compared to analogous indexes in rats with AP + DM with EDI (Kruscall-Wallis criteria).

A 37.3 % increase in lactate levels ($p<0.01$) and a 17.1 % decrease in pyruvate levels ($p<0.05$) were found compared with similar indexes in intact rats. The lactate-to-pyruvate ratio in rats with AP was equal to 15.88, which indicated a significant increase of 1.66 times ($p<0.05$).

Lactate content was higher (by 89.8 %), and the pyruvate content was lower (by 35.8 %) in rats with AP with concomitant type I DM about the same intact indexes (in all cases $p<0.001$). At the same time, lactate and pyruvate content changes were significant compared to the corresponding indexes in rats with AP (in all cases $p<0.05$). A significant increase in 3 times of lactate to pyruvate ratio in the kidneys

of this group of animals was noted compared to the normal value and 1.79 times compared to the rats' group with AP ($p<0.05$ in all cases).

Significant changes in investigated indexes were preserved relative to those in intact rats and rats with AP due to EDI use in animals with AP and concomitant type I DM. One could not see any changes between these indexes and the same in rats with AP and I type DM without pharmacological correction ($p>0.05$).

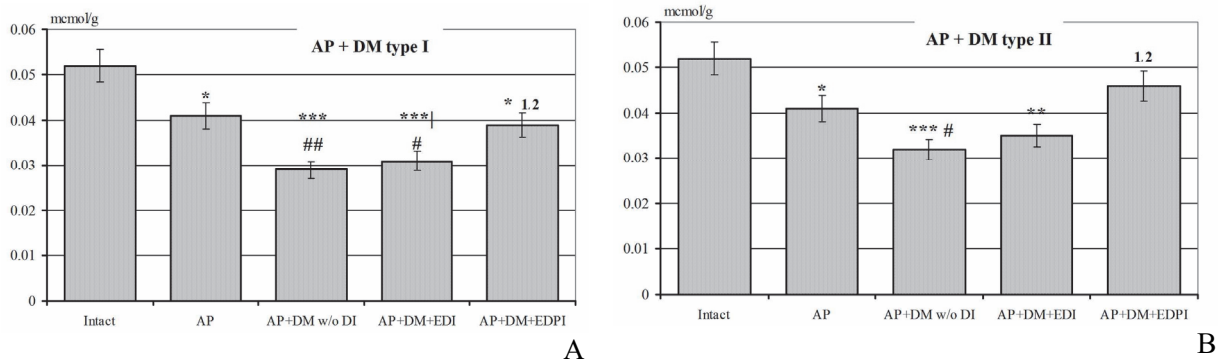
The EPDI use in animals with AP and concomitant type I DM contributed to a lactate content decrease (by 24.6 %) and pyruvate content increase (by 19.3 %) about the same indexes in rats with AP and type I DM with EDI ($p<0.05$ in all cases). The lactate-to-pyruvate ratio inside the kidneys of this group of animals was significantly reduced to 14.57, which was 1.59 times less compared with the same index in rats with EDI ($p<0.05$).

Significant changes in energy balance were registered in rats with AP on the background of type II DM: lactate levels increased by 67.8 % and 22.2 %, respectively, and pyruvate levels decreased by 31.7 % and 17.6 %, respectively, comparing with corresponding indexes in intact rats ($p<0.001$ in all cases) and in rats with AP without treatment ($p<0.05$ in all cases).

EDI use did not cause significant changes in investigated parameters. EDPI use in rats with AP and concomitant type II DM resulted in a significant lactate level decrease (by 21.9 %) and pyruvate level increase (by 21.7 %) relative to similar data in rats with EDI ($p<0.05$ in all cases). The lactate-to-pyruvate ratio in the kidneys of animals in these conditions was equal to 12.41, which was 1.9 times less than in rats with EDI ($p<0.05$).

EDPI use in animals with AP and concomitant types I and II DM led to a free NAD/NADH ratio equal to 621.62 and 729.73, respectively, which was significantly higher compared with similar indexes in rats of these groups without pharmacological influence and EDI administration ($p<0.05$ in all cases).

The level of GP in the kidneys of rats with AP decreased relatively to normal indexes ($p<0.05$; Fig. 1).



A B

Fig. 1. Glucose-6-phosphate content in kidneys of rats with acute pyelonephritis with comorbid type I (A) and type II (B) diabetes mellitus under the drug influence.

Notes: * – $p<0.05$, ** – $p<0.01$ and *** – $p<0.001$ – significant differences of the studied indexes compared to analogous control indexes; # – $p<0.05$ and ## – $p<0.01$ – significant differences of the studied indexes compared to analogous indexes in rats with AP; 1 – $p<0.05$ – significant differences of the studied indexes compared to analogous indexes in rats with AP + DM without drug influence; 2 – $p<0.05$ – 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).

The content of GP in kidneys of rats with AP and concomitant types I and II DM without treatment decreased by 44.2 % and 38.5 %, respectively, compared to the normal values ($p<0.001$ in all cases) and by 29.3 % and 22.0 %, respectively, relative to the same indexes in rats with AP ($p<0.05$ in all cases).

An expressed increase in GP content in the kidneys of rats was recorded after the EPDI administration was compared with similar data in rats with AP and concomitant diabetes of both types ($p<0.05$ in all cases).

The content of ATP in the kidneys of rats with AP was reduced by 78.6 % ($p<0.05$; Table 2). The content of ATP in the kidneys of rats with AP and concomitant types I and II DM without the treatment was significantly less (by 44.0 % and 39.6 %, respectively) compared to normal values ($p<0.01$ in all cases). At the same time, the level of this macroergic compound was reduced in rats with type I DM by 28.7 % and in rats with type II DM by 23.1 % compared with corresponding values in rats with AP ($p<0.05$ in all cases).

Table 2

The content of ATP and ADP and ATP/ADP ratio in kidneys of rats with acute pyelonephritis with comorbid diabetes mellitus under the drug's influence

Investigated 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				
ATP, μmol/g	1.82±0.14	1.43±0.12*	1.02±0.07***††	1.10±0.07***†	1.38±0.11*‡#
ADP, μmol/g	0.93±0.06	0.84±0.06	0.68±0.04*†	0.72±0.05*	0.82±0.05‡
ATP/ADP	1.96	1.70	1.50*	1.53	1.68
	Acute pyelonephritis + diabetes mellitus type II				
ATP, μmol/g	1.82±0.14	1.43±0.12*	1.12±0.08***†	1.23±0.09**	1.57±0.13‡‡#
ADP, μmol/g	0.93±0.06	0.81±0.07	0.72±0.04*	0.76±0.05*	0.87±0.06‡
ATP/ADP	1.96	1.70	1.56*	1.62	1.80

Notes: * – $p<0.05$, ** – $p<0.01$ and *** – $p<0.001$ – significant differences of the studied indexes compared to analogous control indexes; † – $p<0.05$ and †† – $p<0.01$ – significant differences of the studied indexes compared to analogous indexes in rats with AP; ‡ – $p<0.05$ and ‡‡ – $p<0.001$ – significant differences of the studied indexes compared to analogous indexes in rats with AP + DM without drug influence; # – $p<0.05$ – 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).

The ATP content in kidneys of animals with AP and concomitant type I and II DM after EDI user did not change, however, after EPDI administration, we registered an expressed increase of studied index by 25.5 % and 27.6 %, respectively, compared with the same indexes in rats with AP and concomitant types I and II DM with EDI ($p<0.05$ in all cases). The investigated index was 1.35 times and 1.40 times, respectively, higher compared with corresponding indexes in rats with DM without pharmacological correction ($p<0.05$ in all cases).

The ADP content was significantly less in rats with AP on the background of type I DM (by 26.9 %) and type II DM (by 22.6 %) when compared with the same control data ($p<0.05$ in all cases). One could see a significant decrease in ADP content only in the case of type I DM ($p<0.05$).

Intrarenal ADP content underwent significant changes only in the case of EPDI administration; this index in these conditions significantly exceeded the corresponding data in rats with AP and concomitant type I and type II DM by 20.6 % and 20.8 %, respectively ($p<0.05$ in all cases).

The ATP/ADP ratio was significantly less in rats with AP and type I DM (by 23.5 %) and type II DM (by 20.4 %) compared with the control data ($p<0.05$ in all cases). The ATP/ADP ratio tended to increase but did not reach statistical significance after EPDI use in rats with AP and concomitant types I and II DM ($p>0.05$).

We believe that the discussion of data obtained should be divided into two main blocks. The first of them concerns the energy deficiency in kidneys' pathophysiological mechanisms in conditions of AP and concomitant DM.

The data obtained from analysis of the first block demonstrates the following three main pathobiochemical changes in the kidney tissue of rats in the modeled comorbid conditions. The lactate content significantly increased, and oxidized pyruvate content decreased in lactatedehydrogenase system in these conditions.

Additionally, a free NAD/NADH ratio decrease was also recorded. This ratio and the state of adenine nucleotide phosphorylation, is a regulatory index that determines the carbohydrate metabolism expression. Decreased free NAD/NADH ratio will activate pyruvatecarboxylase with oxaloacetate formation and promote gluconeogenesis in rats' kidneys. One could also add the suppression of pyruvatedehydrogenase activity due to its inactive form creation [10].

The following fact we proved is the decrease of glucose-6-phosphate content in kidneys in the conditions of the modeled comorbid pathology. Energy deficiency in this aspect is demonstrated by the deficiency of an extremely important form of phosphorylated glucose in the processes of energy metabolism - glucose-6-phosphate [13]. Glucose-6-phosphate is known to determine the kidney parenchyma energy supply due to glycolytic processes. Therefore, the reduced concentration of glucose-6-phosphate – the initial product of glycolysis – in conditions of AP and especially with types I and II DM indicates the glycolysis inhibition inside the rats' kidneys [10].

It is important that glucose-6-phosphate is a substrate for glucose-6-phosphate dehydrogenase – a key enzyme of the pentosephosphate cycle – that regenerates NADPH, which is essential for the glutathione

detoxification system. Additionally, the pentosephosphate cycle produces ribose and ribose-5-phosphate, which are extremely important for nucleic acid synthesis [11].

Intrarenal glucose-6-phosphate content decrease in conditions of AP and concomitant DM might occur due to oxidative stress inside kidney tissues, which can "trigger" the following cascade of pathobiochemical and pathophysiological processes – carbohydrate metabolism failure and imbalance of energy metabolism anaerobic and aerobic processes of ratio [14].

These findings are supported by studies showed that decreased insulin effects in tissues can cause pyruvatedehydrogenase activity suppression, which, in turn, increases the pyruvate-to-lactate conversion. Hexokinase activity change that participates in glucose phosphorylation in case of diabetic hyperglycemia may also be associated with glucose-6-phosphate decreased levels, thus leading to intrarenal glucose utilization decrease [6, 10, 14].

The enhancement of energy-consuming reactions in rats with AP is another indicative result of the study that is proved by a decrease in the ATP/ADP ratio: these changes are evident in conditions of AP comorbidity with DM. It should be mentioned that ATP has a regulatory impact on glomerular filtration and tubular transport and, therefore, plays an important role in renal autoregulation [4].

Resuming, we stress lactate to pyruvate ratio increase and both GP and ATP levels decrease, contributing to glucose oxidation decrease and gluconeogenesis intensification throughout the inflammatory process in kidneys in the presence of concomitant DM. These pathobiochemical changes may exacerbate the negative impact of hyperglycemia on kidney function during acute inflammatory damage, which must be considered when composing a complex pathogenetically oriented pharmacological correction.

We will focus on the following positions while discussing the second block of data obtained. The first is pharmacological drug selection for EPDI in animals with AP with hyperglycemic states on the background associated with the succinate-containing compound 2-ethyl-6-methyl-3-hydroxypyridine succinate, which mechanisms of nephroprotective efficacy are antioxidant, antihypoxic and membrane-protective action. This compound is a succinate donor for the respiratory chain and promotes the succinateoxidase oxidation pathway activation in mitochondria, thus exhibiting mitoprotective activity, and also contributing to intracellular ATP concentration normalization [15]. Succinate-containing drugs' high efficacy was proved in liver and kidney functional activity restoration with high-fat diet prolonged intake in patients with internal organ disorders of inflammatory and hypoxic genesis [15]. We choose the drug "Nuklex" due to the presence of ribonucleic acid in its composition and its antimicrobial and energotropic properties [12].

The second was a significant decrease in lactate concentration, and the process of normalizing pyruvate levels in the kidneys was proved in pathogenetically oriented pharmacological correction conditions. Our combined administration of succinate-containing compounds and ribonucleic acid donors caused a restorative impact on energy metabolism indexes in kidney tissue in AP, which is complicated by DM. A similar effect was absent in conditions of simple pharmacological influence without "Armadin" and "Nuklex" sanogenetic effects.

The mechanism of EPDI influence on the level of oxy- and ketoacids in the kidneys in AP and experimental diabetes can be assumed to be their direct regulatory impact on energy metabolism, especially on the pyruvatedehydrogenase complex and on the mitochondria of the tissue structural and functional parameters [5] by reducing carbonyl- and oxidative stress which was shown in our previous publications.

Thus, the results of the study can be interpreted as an experimental background of the reasonability of succinate-containing compounds and ribonucleic acid donors' co-administration in clinical conditions to normalize lactate, pyruvate, and energy potential (ATP/ADP) content in patients with AP with concomitant diabetic kidney damage.

Conclusions

1. Energetic balance changes (lactate level increase and pyruvate, glucose-6-phosphate, and ATP content decrease) were found in kidneys or rats with AP. These indexes changes indicate disturbances in energy metabolism, the adenine nucleotide system, and the development of intrarenal energy deficiency in rats with AP.

2. Further progression of energy metabolism disorders was found in the kidneys of rats with AP with concomitant DM, especially of the I type. Such energetic chaos manifested in the form of ATP reserves depletion, which may be associated with ATP-impaired synthesis. An oxidative potential decrease,

in turn, and the possibility of energy metabolism change onto the gluconeogenesis pathway intensify hyperglycemia, contributing to both intrarenal hypoxia and acidosis development.

3. Succinate-containing compounds and a ribonucleic acid donor combined administration cause a restorative impact on energy metabolism indexes in kidney tissue in AP complicated by DM.

4. Results of the study served as experimental background of the reasonability of succinate-containing compounds and ribonucleic acid donors co-administration in clinical conditions to normalize lactate, pyruvate, and energy potential content in patients with AP with concomitant diabetic kidney damage.

Prospects for further research aimed to perform acute pyelonephritis comorbid with hyperglycemia new pathogenetically oriented methods of pharmacological treatment using compounds with energy restorative efficacy and antioxidant, antihypoxic, and membrane-stabilizing impact.

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