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Features of Bcl2 and p53 proteins synthesis in pancreatic islets of normotensive and hypertensive rats with streptozotocin-induced diabetes

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

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In our previous studies it was established that the remodeling of pancreatic islets with decreasing β-cell population density is formed in hypertensive SHR rats. The imbalance between the synthesis of proapoptotic and antiapoptotic factors may be one of the possible causes of disturbed formation of the endocrinocyte population in the pancreas.

The aim of the research was to study the parameters of Bcl2 and p53 proteins synthesis in pancreatic islets in normotensive and hypertensive rats in the streptozotocin-induced diabetes mellitus development.

Materials and methods. The study was performed on 30 normotensive male Wistar rats (systolic BP = 105.0 ± 1.1 mm Hg) and 25 hypertensive SHR rats (systolic BP = 155.7 ± 0.9 mm Hg) with fasting normoglycemia (4.73 ± 0.10 mmol/l). Bcl2 and p53 proteins were detected in histological pancreas sections by immunofluorescence method. The relative area of Bcl2- and p53-immunopositive material, concentration of proteins in endocrinocytes, their content in the islets and apoptosis index p53/Bcl2 were analyzed in pancreatic islands.

Results. The area of relative immunofluorescence to the Bcl2 protein was 2 times less, and the protein content was 3 times lower in pancreatic islets of hypertensive rats (SHR) compared with normotensive Wistar rats. At the same time, no statistical differences in the area of the immunopositive material to the p53 protein and its content in the islets between the experimental groups were revealed. The development of streptozotocin-induced diabetes in Wistar rats was accompanied by approximately 2-fold decrease in the Bcl2 protein expression in pancreatic islets, a significant increase in the specific content of p53 protein and a 3.8-fold increase in the apoptosis index of p53/Bcl2. In pancreatic islets of SHR rats, diabetes mellitus development was accompanied by 2-fold increase in the specific content of the proapoptotic protein p53 without the reduction of the antiapoptotic protein Bcl2 synthesis. At the same time, the p53/Bcl2 apoptosis index in SHR rats remained statistically higher than in Wistar rats.

Conclusions. Endocrine cells of pancreatic islets of SHR rats are characterized by the prevalence of proapoptotic protein p53 expression as compared with Wistar line normotensive rats. The development of streptozotocin diabetes in Wistar rats leads to a significant decrease in the number of endocrinocytes synthesizing the antiapoptotic protein Bcl2. At the same time, an increase in the synthesis of the proapoptotic protein p53 in endocrinocytes in diabetes is observed both in normotensive and in hypertensive rats.

Ключові слова: гіпертонічна хвороба, цукровий діабет, панкреатичні острівці, апоптоз.

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Особливості синтезу білків Bcl2 і p53 в панкреатичних острівцях нормотензивних і гіпертензивних щурів зі стрептозотоцин-індукованим діабетом

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У попередніх дослідженнях встановили, що в гіпертензивних щурів лінії SHR формується ремоделювання панкреатичних острівців зі зменшенням щільності популяції β-клітин. Однією з можливих причин порушення формування популяції ендокриноцитів підшлункової залози може бути дисбаланс між синтезом проапоптотичних та антиапоптотичних факторів.

Мета роботи – вивчити параметри синтезу білків Bcl2 і p53 в панкреатичних острівцях у нормотензивних і гіпертензивних щурів при розвитку стрептозотоцин-індукованого цукрового діабету.

Матеріали та методи. Дослідження здійснили на 30 нормотензивних самцях щурів лінії Wistar (систолічний АТ = 105,0 ± 1,1 мм рт. ст.) і 25 гіпертензивних щурах лінії SHR (систолічний АТ = 155,7 ± 0,9 мм рт. ст.) з нормоглікемією натще (4,73 ± 0,10 ммоль/л). У гістологічних зрізах підшлункової залози імунофлуоресцентним методом виявляли білки Bcl2 і p53. У панкреатичних острівцях аналізували відносну площу Bcl2- і p53-імунопозитивного матеріалу, концентрацію білків в ендокриноцитах, їхній вміст в острівцях та індекс апоптозу p53/Bcl2.

Результати. У панкреатичних острівцях гіпертензивних щурів лінії SHR лінії площа відносної імунофлуоресценції до білка Bcl2 була вдвічі меншою, а вміст білка втричі нижчим, ніж у нормотензивних тварин лінії Wistar. Статистичні відмінності площі імунопозитивного матеріалу до білка p53 і його вмісту в острівцях між експериментальними групами не виявили. Розвиток стрептозотоцинового діабету в нормотензивних щурів лінії Wistar супроводжувався зменшенням експресії білка Bcl2 в панкреатичних острівцях приблизно вдвічі, істотним збільшенням питомого вмісту білка p53 та збільшенням індексу апоптозу p53/Bcl2 у 3,8 раза. У панкреатичних острівцях гіпертензивних щурів лінії SHR розвиток діабету супроводжувався 2-разовим збільшенням питомого вмісту проапоптотичного білка p53 без редукції синтезу антиапоптотичного білка Bcl2. Індекс апоптозу p53/Bcl2 у щурів лінії SHR зберігав статистично вищі значення, ніж у щурів лінії Wistar.

Висновки. Для ендокриноцитів панкреатичних острівців щурів лінії SHR характерне переважання експресії проапоптотичного білка p53 порівняно з нормотензивними щурами лінії Wistar. Розвиток стрептозотоцинового діабету в щурів лінії Wistar призводить до суттєвого обмеження кількості ендокриноцитів, що синтезують антиапоптотичний білок Bcl2. Збільшення синтезу проапоптотичного білка p53 в ендокриноцити при діабеті визначили і в нормотензивних, і в гіпертензивних щурів.

Особенности синтеза белков Bcl2 и p53 в панкреатических островках нормотензивных и гипертензивных крыс со стрептозотоцин-индуцированным диабетом

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Ключевые слова: гипертоническая болезнь, сахарный диабет, панкреатические островки, апоптоз.

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В предыдущих исследованиях установлено, что у гипертензивных крыс линии SHR формируется ремоделирование панкреатических островков с уменьшением плотности популяции β-клеток. Одной из возможных причин нарушения формирования популяции эндокриноцитов поджелудочной железы может быть дисбаланс между синтезом проапоптотических и антиапоптотических факторов.

Цель работы – изучить параметры синтеза белков Bcl2 и p53 в панкреатических островках у нормотензивных и гипертензивных крыс при развитии стрептозотоцин-индуцированного сахарного диабета.

Материалы и методы. Исследование проведено на 30 нормотензивных самцах крыс линии Wistar (систолическое АД = 105,0 ± 1,1 мм рт. ст.) и 25 гипертензивных крысах линии SHR (систолическое АД = 155,7 ± 0,9 мм рт. ст.) с нормогликемией натощак (4,73 ± 0,10 ммоль/л). В гистологических срезах поджелудочной железы иммунофлуоресцентным методом выявляли белки Bcl2 и p53. В панкреатических островках анализировали относительную площадь Bcl2- и p53-иммунопозитивного материала, концентрацию белков в эндокриноцитах, их содержание в островках и индекс апоптоза p53/Bcl2.

Результаты. В панкреатических островках у гипертензивных крыс линии SHR линии площадь относительной иммунофлуоресценции к белку Bcl2 была в 2 раза меньше, а содержание белка в 3 раза ниже, чем у нормотензивных животных линии Wistar. Статистические отличия площади иммунопозитивного материала к белку p53 и его содержания в островках между экспериментальными группами не установлены. Развитие стрептозотоцинового диабета у нормотензивных крыс линии Wistar сопровождалось уменьшением экспрессии белка Bcl2 в панкреатических островках примерно в 2 раза, существенным нарастанием удельного содержания белка p53 и увеличением индекса апоптоза p53/Bcl2 в 3,8 раза. В панкреатических островках гипертензивных крыс линии SHR развитие диабета сопровождалось 2-кратным нарастанием удельного содержания проапоптотического белка p53 без редукции синтеза антиапоптотического белка Bcl2. Индекс апоптоза p53/Bcl2 у крыс линии SHR сохранял статистически более высокие значения, чем у крыс линии Wistar.

Выводы. Для эндокриноцитов панкреатических островков крыс линии SHR характерно преобладание экспрессии проапоптотического белка p53 по сравнению с нормотензивными крысами линии Wistar. Развитие стрептозотоцинового диабета у крыс линии Wistar приводит к существенному ограничению количества эндокриноцитов, синтезирующих антиапоптотический белок Bcl2. Нарастание синтеза проапоптотического белка p53 в эндокриноцитах при диабете отмечено и у нормотензивных, и у гипертензивных крыс.

Essential hypertension is one of the most common chronic diseases, the incidence of which ranges from 29.0 % in adults to 64.9 % in people over 60 years [1]. Patients with arterial hypertension present the majority of the cardiological group of patients; type 2 diabetes mellitus accompanies from 20 % in the USA to 30 % of cases in Italy [2]. The combination of essential hypertension and diabetes mellitus in patients is known as a metabolic syndrome that increases the clinical severity of single nosologies and worsens the prognosis for life [3]. We reported previously that fasting glycemia does not exceed 5.5 mmol/L in 2/3 of the SHR rats with hereditary arterial hypertension [4]. Nevertheless, the signs of pancreatic islet cytoarchitectonics are revealed: the decrease in the population density of β-cells [5,6] and an increase in the number of α-cells in the pancreas[7]. It is proved that diabetes mellitus modeling with streptozotocin in Wistar rats normally leads to the formation of stable hyperglycemia, decrease in β-endocrinocytes number [8–10] and a rise in α-cells quantity in the pancreas [10–12].

We have demonstrated that streptozotocin-induced diabetes in SHR rats also leads to hyperglycemia, while a lesser degree of β-cell death is noted in the pancreas than in normotensive Wistar rats [9]. Moreover, the development of diabetes mellitus in SHR rats leads to a decrease in the population density of α-cells in the pancreas, in contrast to Wistar rats [9]. We suppose that the number of endocrinocytes in the pancreas under normal and pathological conditions can be affected not only by β-cytopathic factors, such as streptozotocin, antibodies to intra-islet antigens, hypoxia, but also the level of intracellular expression of proapoptotic and antiapoptotic factors, such as p53 and Bcl2 proteins [13,14].

The aim

The aim of the research was to study the parameters of Bcl2 and p53 proteins synthesis in pancreatic islets in normotensive and hypertensive rats subjected to streptozotocin-induced diabetes mellitus development.

Materials and methods

The research was carried out on 30 normotensive male rats of Wistar line (systolic BP = 105.0 ± 1.1 mm Hg)

and 25 hypertensive rats of SHR line (systolic BP = 155.7 ± 0.9 mm Hg) with fasting normoglycemia (4.73 ± 0.10 mmol/L). The animals were kept in standard vivarium conditions under natural light without restriction of access to water and food. The studies were conducted in accordance with the requirements of international principles of the European Convention (Strasbourg, 1985). Diabetes mellitus was modeled in 15 Wistar rats and 10 SHR rats by a single intraperitoneal injection of streptozotocin (SIGMA Chemical, USA) in a dose of 50 mg/kg dissolved in 0.5 ml of 0.1 M citrate buffer (pH = 4.5). 3 weeks after, the concentration of glucose in the blood was measured in animals with the help of GlucoCard-II glucometer (Japan), and systolic blood pressure was measured with the help of BP-2000 non-invasive pressure control system (Visitech Systems, USA).

The pancreas was extracted after decapitation of experimental animals under thiopental anesthesia (50 mg/kg), fixed in Bouin solution (20 hours) and poured into paraplast (McCormick, USA) after standard histological processing. Serial histological slices of the pancreas 5 μm thick were dewaxed and unmasked in a citrate buffer solution (pH = 9.0) in the PT-module (Thermo Scientific, USA). Bcl2 and p53 proteins in pancreatic islets were detected by immunofluorescence method using antibodies produced by Santa Cruz Biotechnology (USA). Primary antibodies were incubated in dilution 1:200 (wet chamber, T = +4 °C, 24 hours), secondary antibodies conjugated with FITC were incubated in dilution 1 : 64 (wet chamber, T = +37 °C, 45 min).

The slices were washed in phosphate buffer and then enclosed in a mixture of glycerin/phosphate buffer (9:1). Specificity of antibody binding was controlled in similar way, except for incubation with primary antibodies. Immunofluorescence reaction was studied using the AxioImager-M2 fluorescence microscope (Carl Zeiss, Germany) with the digital camera AxioCam-HRm (Carl Zeiss, Germany) and with the use of the high-emission 38HE filter (λ_{ex} = 470/40 nm, λ_{em} = 525/50 nm) (Carl Zeiss, Germany). Quantitative analysis of the immunofluorescence reaction was carried out with the help of AxioVision-4.8.2 digital image analysis system (Carl Zeiss, Germany). At least 75 pancreatic islets were examined in each series and the following parameters were measured and calculated:

1) the relative area of the immunopositive material (the percentage of the immunopositive material in the islet area);

2) the concentration of proteins in endocrinocytes (the module of the logarithm of the background fluorescence to the fluorescence of immunopositive material ratio, expressed in relative units of fluorescence – U_{IF});

3) the protein content in pancreatic islets (calculated as the product of the specific concentration of proteins and immunopositive material area in 1 cm^2 of the area of the islets, expressed in U_{IF} / cm^2);

4) apoptosis index (the ratio of p53 protein content to Bcl2 protein content in pancreatic islets).

Experimental data were processed with Excel 2003 (Microsoft Corp.) statistical analysis software package. The reliability of the differences between the experimental groups was assessed using the Student's criterion t, considering the differences to be reliable at $P < 0.05$.

Results

The development of streptozotocin diabetes led to the formation of hyperglycemia both in normotensive Wistar rats (17.69 ± 1.10 mmol/L) and in SHR rats with hereditary hypertension (11.45 ± 0.89 mmol/L). Earlier, we attributed this to significant reduction of the α-endocrinocyte pool in the pancreas of hypertensive rats, which does not lead to excessive glucagon synthesis, which is observed in Wistar rats along with of intensive α-cells proliferation [9].

The area of relative immunofluorescence to the Bcl2 protein was 2 times less in pancreatic islets, in hypertensive rats than in normotensive animals, while the area of p53 protein immunopositive material was almost the same (*Table 1*).

Despite the fact that the parameters of protein concentration in the cells in normo- and hypertensive rats did not statistically differ, their ratio indicated the predominance of pro-apoptotic p53 protein expression in the endocrinocytes in SHR rats (*Table 2*).

Calculation of the Bcl2 protein content in pancreatic islets demonstrated its 3-fold decrease in hypertensive rats in comparison with normotensive animals (*Table 3*). The p53 protein content in the islets of both animal lines did not statistically differ. It is possible that low indices of Bcl2 antiapoptotic protein expression in pancreatic endocrinocytes in SHR line rats may be one of the reasons for the decrease in the β-cell population in these animals [5,6].

The development of experimental diabetes in normotensive rats led to a 2-fold decrease in the area of Bcl2 immunopositive material in pancreatic islets accompanied with an increase in the area of immunoreactivity to p53 protein by 55 %. In contrast, there was an increase in immunoreactivity both to Bcl2 and p53 protein by more than 50 % in pancreatic islets of hypertensive animals (*Table 1*).

The development of diabetes led to an increase in the concentration of p53 protein in endocrinocytes in normotensive and hypertensive rats by 24 % and 31 %, respectively. At the same time, the development of diabetes in normotensive animals did not affect the concentration of Bcl2 protein in the cells, while in hypertensive animals a decrease in the concentration of Bcl2 protein by 33 % was observed (*Table 2*). This resulted in the fact that the index of apoptosis – Bcl2/p53 in endocrinocytes in normotensive animals with diabetes decreased only by 12 % ($P < 0.02$), and in hypertensive rats – by 40 % ($P < 0.001$).

Changes in the parameters of Bcl2 and p53 proteins immunoreactivity in the diabetes mellitus development in normotensive rats resulted in a 40 % decrease in the specific content of the antiapoptotic Bcl2 protein in pancreatic islets, combined with 2.3-fold increase in the specific content of the proapoptotic p53 protein (*Table 3*). Whereas, the development of diabetes in hypertensive rats of resulted only in 2-fold increase in the specific content of the p53 protein in the pancreatic islets as compared with the control group. Moreover, the development of diabetes in normotensive animals resulted in the increase of the apoptosis index by 3.84 times, while in hypertensive

Table 1. Relative area (%) of immunopositive material in pancreatic islets (M ± m)

Parameter	Normotensive rats		Hypertensive rats	
	Control, n = 91	Diabetes, n = 76	Control, n = 83	Diabetes, n = 78
Bcl2	4.966 ± 0.728#	2.798 ± 0.184*	2.475 ± 0.144*	3.771 ± 0.597#
p53	2.157 ± 0.195	3.344 ± 0.258*#	2.123 ± 0.180	3.209 ± 0.225*#
Bcl2 / p53	2.302 ± 0.083#	0.836 ± 0.074*#	1.165 ± 0.096*	1.175 ± 0.095*

Reliability P < 0.05 of differences in comparison with normotensive (*) and hypertensive (#) rats without diabetes; **n:** the number of pancreatic islets that were examined.

Table 2. Protein concentration (U_{IF}) in endocrinocytes (M ± m)

Parameter	Normotensive rats		Hypertensive rats	
	Control, n = 91	Diabetes, n = 76	Control, n = 83	Diabetes, n = 78
Bcl2	0.611±0.079	0.664±0.040#	0.514±0.011	0.397 ± 0.019*#
p53	0.449 ± 0.017	0.556 ± 0.042*#	0.448±0.021	0.587 ± 0.030*#
Bcl2 / p53	1.360 ± 0.050	1.194 ± 0.048*	1.147 ± 0.020*	0.676 ± 0.052*#

Significance (P < 0.05) of differences in comparison with normotensive (*) and hypertensive (#) rats without diabetes; **n:** the number of pancreatic islets that were examined.

Table 3. Protein content (U_{IF}/cm^2) in pancreatic islets (M ± m)

Parameter	Normotensive rats		Hypertensive rats	
	Control, n = 91	Diabetes, n = 76	Control, n = 83	Diabetes, n = 78
Bcl2	3.570 ± 0.203#	2.118 ± 0.265*#	1.271 ± 0.079*	1.549 ± 0.232*
p53	0.984±0.102	2.242 ± 0.372*#	1.063 ± 0.133	2.104 ± 0.252*#
apoptosis index p53/Bcl2	0.275 ± 0.059#	1.058 ± 0.077*#	0.836 ± 0.026*	1.358 ± 0.065*#

Significance (P < 0.05) of differences in comparison with normotensive (*) and hypertensive (#) rats without diabetes; **n:** the number of pancreatic islets that were examined.

rats this index increased only by 1.62 times. However, in hypertensive animals the apoptosis index in pancreatic islets was still significantly higher (P < 0.05) than in normotensive rats.

Discussion

The data obtained in the current research indicate that the development of experimental diabetes mellitus leads to a significant decrease in quantity of the endocrinocytes that synthesize the anti-apoptotic protein Bcl2 only in normotensive rats. At the same time, an increase of proapoptotic p53 protein synthesis in endocrinocytes in diabetes is observed both in normotensive and hypertensive rats.

It is known that Bcl-2 family of proteins include proteins both with anti-apoptotic and pro-apoptotic activity. Such proteins as Bcl2-protein (Bcl2), B-cell lymphoma-extra-large (Bcl-xL), Bcl-2-like protein 2 (Bcl-w), Bcl-2-like protein 10 (Bcl-B), myeloid cell leukemia 1 (MCL-1) and Bcl-2 related gene A1 (A1) prevent apoptosis [15]. They realize their anti-apoptotic effect at the mitochondrial level, and also block the activity of caspases and proapoptotic proteins Bcl-2 family members in the cell [16]. Other proteins of Bcl-2 family such as Bcl-2-associated X protein (Bax) and Bcl-2 antagonist killer 1 (Bak), in contrast, have a proapoptotic influence [15,16]. It is believed that the balance between pro- and anti-apoptotic proteins of the Bcl-2 family is a key parameter that determines the choice between life and death for a cell [17]. It has been established that in type 1 and type 2 diabetes Bcl2 production increases in β-cells along with other molecular regulators of apoptosis, [16], that might have a protective value and to some extent reflect the compensatory potential of β-endocrinocytes in diabetes.

It was noted that apoptosis of β-cells in diabetes, caused by overproduction of pro-inflammatory cytokines and a decrease in the mitochondrial transmembrane potential in endocrinocytes is inhibited by stimulation of Bcl2 expression [18].

A product of the TP53 gene (tumor suppressor gene) activity – p53 protein is an important regulator of apoptosis in cells along with the Bcl-2 family proteins [17]. Being a kind of "guardian of the genome", the p53 protein initiates apoptosis in DNA damage caused by radiation, chemical agents, reactive oxygen species, hypoxia, and other injuring factors. Furthermore, the p53 protein realizes its proapoptotic potential by inducing pro-apoptotic proteins of the Bcl-2 family: Bax, PUMA (p53 upregulated modulator of apoptosis) and Noxa (phorbol-12-myristate-13-acetate-induced protein 1) [17,19]. It is proved that p53 protein can trigger β-cell dysfunction and suppress insulin secretion in them [19]. At the same time, inhibition of p53 activity or knockout of the TP53 gene in mice preclude apoptosis of β-endocrinocytes and prevent insulin resistance development in adipocytes [19].

Therefore, the estimation of the balance between the synthesis of anti- and proapoptotic factors in pancreatic endocrinocytes can be a prognostic factor for assessing the resistance of β-endocrinocytes to the action of pathogenic factors, as well as for assessment the risk of diabetes mellitus development. In the present study, we revealed a deficiency of anti-apoptotic potential caused by a decrease in the Bcl2 protein synthesis in pancreatic islets that led to an increase in the endocrinocyte apoptosis index in normoglycemic hypertensive SHR rats to the level typical to normotensive Wistar rats with streptozotocin-induced diabetes. This fact to some extent explains the low specific density of the β-endocrinocyte population in spontaneously hypertensive rats compared with normotensive Wistar animals [5,6]. In addition to that, adaptive hypobaric hypoxic training of Wistar rats with streptozotocin-induced diabetes increases the anti-apop-

totic potential of β-cells and reduces the index of apoptosis that ultimately leads to a rise in β-endocrinocytes pool, increase of insulin synthesis in them and a decrease in glycemia level [13,14].

Conclusions

1. The endocrinocytes of pancreatic islets in normotensive Wistar rats demonstrate higher level of the anti-apoptotic protein Bcl2 synthesis than hypertensive rats of the SHR line, while the level of the pro-apoptotic protein p53 expression is almost the same.

2. Experimental diabetes mellitus development in normotensive Wistar rats is accompanied by 2-fold decrease in the expression of Bcl2 protein in pancreatic islets, a significant increase in the specific content of p53 protein, and an increase in the p53/Bcl2 apoptosis index by 3.8 times.

3. The development of diabetes in SHR rats is accompanied by 2-fold increase in the specific content of the pro-apoptotic protein p53 in the pancreatic islets without reduction of anti-apoptotic protein Bcl2 synthesis. At the same time, the p53/Bcl2 apoptosis index in SHR rats remains statistically higher than in Wistar rats.

Prospects for further research. Further study of the mechanisms of endocrinocyte death in diabetes, due to the interaction of key molecular regulators of apoptosis β-cells such as Bcl2, Bcl-xL, Bax, Bak, and MST1 proteins are proposed.

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References

[1] Yoon, S. S., Carroll, M. D., & Fryar, C. D. (2015). Hypertension Prevalence and Control among Adults: United States, 2011-2014. *NCHS Data Brief, 220*, 1-8.
[2] Seferovic, P. M., Petrie, M. C., Filippatos, G. S., Anker, S. D., Rosano, G., Bauersachs, J., . . . McMurray, J. J. V. (2018). Type 2 diabetes mellitus and heart failure: a position statement from the Heart Failure Association of the European Society of Cardiology. *European Journal of Heart Failure, 20*(5), 853-872. https://doi.org/10.1002/ejhf.1170
[3] Wou, C., Unwin, N., Huang, Y. D., & Roglic, G. (2019). Implications of the growing burden of diabetes for premature cardiovascular disease mortality and the attainment of the Sustainable Development Goal target 3.4. *Cardiovascular Diagnosis and Therapy, 9*(2), 140-149. https://doi.org/10.21037/cdt.2018.09.04
[4] Gancheva, O. V., Kolesnik, Yu. M., Abramova, T. V., Samoylenko, N. Yu., & Abramov, A. V. (2013). Metabolic disturbances in hypertensive SHR rats. *Klinichna farmatsiia, 17*(4), 56-58.
[5] Abramova, T. V. (2016). The distribution of the islets of Langerhans in pancreas of euglycemic spontaneously hypertensive rats. *Pathologia*(1), 19-21. https://doi.org/10.14739/2310-1237.2016.1.72359
[6] Abramova, T. V., & Kolesnyk, Y. M. (2016). The features of beta-cells organization in the pancreas of spontaneously hypertensive rat (SHR). *Pathologia*(3), 4-8. https://doi.org/10.14739/2310-1237.2016.3.86931
[7] Abramova, T. V., & Kolesnyk, Y. M. (2017). Osobennosti organizatsii populyatsii al'fa-kletok v podzheludochnoi zheleze u krys so spontannoi gipertenzii (SHR) [Features of the alpha-cell population organization in pancreas of spontaneously hypertensive rats (SHR)]. *Pathologia*(2), 124-128. [in Russian]. https://doi.org/10.14739/2310-1237.2017.2.109249
[8] Abramova, T. V., Kolesnik, Yu. M., & Ivanenko, T. V. (2017). Funktsional'noe sostoyanie b-kletok podzheludochnoi zhelezy u krys so spontannoi gipertenzii (SHR) pri eksperimental'nom diabete [Functional status of b-cells in pancreas of spontaneously hypertensive rats with experimental diabetes]. *Aktualni Problemy Suchasnoi Medytsyny*, 4 (60), 8-12. [in Russian].
[9] Abramova, T., Kolesnik, Y., & Ivanenko, T. (2018). Kolichestvennyye izmeneniya populyatsii endokrinotsitov podzheludochnoy zhelezy u krys linii SHR na fone razvitiya streptozototsin-indutsirovannogo diabeta [Quantitative changes in the pancreatic endocrinocyte population in SHR rats against the background of the development of streptozotocin-induced diabetes]. *Klinichna ta eksperymentalna patolohiia*, 4(66), 8-14. [in Russian]. https://doi.org/10.24061/1727-4338XVE466.2018.181
[10] Plesner, A., ten Holder, J. T., & Verchere, C. B. (2014). Islet Remodeling in Female Mice with Spontaneous Autoimmune and Streptozotocin-Induced Diabetes. *Plos One, 9*(8). https://doi.org/10.1371/journal.pone.0102843
[11] Li, Z., Karlsson, F. A., & Sandler, S. (2000). Islet loss and alpha cell expansion in type 1 diabetes induced by multiple low-dose streptozotocin administration in mice. *Journal of Endocrinology, 165*(1), 93-99. https://doi.org/10.1677/joe.0.1650093
[12] Zhang, Y., Zhang, Y., Bone, R. N., Cui, W., Peng, J. B., Siegal, G. P., … Wu, H. (2012). Regeneration of pancreatic non-β endocrine cells in adult mice following a single diabetes-inducing dose of streptozotocin. *PloS one*, 7(5), e36675. https://doi.org/10.1371/journal.pone.0036675
[13] Ivanenko, T. V., Abramov, A. V., Kolesnik, Yu. M., Vasilenko, G. V. (2011). Endokrinnyi status i uroven' ekspressii belkov Bcl-2 i p53 v pankreaticheskikh ostrovkakh u krys s eksperimental'nym sakharnym diabetom [Endocrine status and expression level of Bcl-2 and p53 proteins in pancreatic islets in rats with experimental diabetes mellitus]. *Pathologia, 8*(2), 18-20. [in Russian].
[14] Ivanenko, T. V., Kolesnyk, Yu. M., & Abramova T. V. (2017). Analiz endokrynnoho statusu ta rivnia ekspresii bilkiv apoptozu i proliferatsii v pankreatychnykh ostrivtsiakh shchuriv z eksperymentalnym tsukrovym diabetom pislia zakinchennia pereryvchastykh hipoksychnykh trenuvan [Analysis of endocrine status and pro-apoptotic protein expression and proliferation in pancreatic islets in rats with experimental diabetes mellitus after intermittent hypoxic training]. *Patolohiia, reabilitatsiia, adaptatsiia, 15*(2), 87-93. [in Ukrainian].
[15] Edlich, F. (2018). BCL-2 proteins and apoptosis: Recent insights and unknowns. *Biochemical and Biophysical Research Communications*, *500*(1), 26-34. https://doi.org/10.1016/j.bbrc.2017.06.190
[16] Lee, S. C., & Pervaiz, S. (2007). Apoptosis in the pathophysiology of diabetes mellitus. *International Journal of Biochemistry & Cell Biology, 39*(3), 497-504. https://doi.org/10.1016/j.biocel.2006.09.007
[17] Hotchkiss, R. S., Strasser, A., McDunn, J. E., & Swanson, P. E. (2009). Mechanisms of Disease Cell Death. *New England Journal of Medicine, 361*(16), 1570-1583. https://doi.org/10.1056/NEJMra0901217
[18] Saldeen, J. (2000). Cytokines induce both necrosis and apoptosis via a common bcl-2-inhibitable pathway in rat insulin-producing cells. *Endocrinology, 141*(6), 2003-2010. https://doi.org/10.1210/en.141.6.2003
[19] Kung, C. P., & Murphy, M. E. (2016). The role of the p53 tumor suppressor in metabolism and diabetes. *Journal of Endocrinology, 231*(2), R61-R75. https://doi.org/10.1530/joe-16-0324