

branching of the arteries. The data on the peculiarities of intramuscular branching of arteries and nerves in the infrahyoid muscles we obtained, as well as the variant anatomy of the infrahyoid area muscles must be taken into account when performing a surgical access to the neck, or when operating on in the anterior cervical region, in particular myoplastic and reconstructive operations, in order to avoid muscle injuries.

DOI 10.31718/2077-1096.20.3.169

UDC 577.1

Kushnir O.Yu., Yaremii I.M.

AGE-RELATED CHANGES OF GLYCOLYTIC ACTIVITY AND ANTIOXIDANT CAPACITY IN THE BLOOD OF ALLOXAN DIABETIC RATS

Bukovinian State Medical University, Chernivtsi

The increasing incidence of type 1 diabetes coupled with advances in treatment of type 1 diabetes has resulted in an unprecedented number of older adults living with and controllable type 1 diabetes. The objective of this experimental study was to assess the impact of aging on the level of basal glycaemia and activities of glucose-6-phosphate dehydrogenase [EC1.1.1.49], pyruvate kinase [EC 2.7.1.40] and glutathione reductase [EC1.6.4.2] in erythrocytes of alloxan-diabetic rats. Methods: We used 100 male Wistar rats, divided into two age groups: I group included- 2-month (adult) animals, and II group was made up of 4-month (old) animals. Diabetes was modelled by injecting the rats with 5% solution of alloxan monohydrate intraperitoneally in a dose of 170 mg/kg. Blood was taken from the tail vein to evaluate the basal glycaemia on 5-th and 47-th day after the alloxan injection. Rats were sacrificed on the 47-th day of the experiment in accordance with the regulations on ethical treatment of vertebrates. The assessment of the activity of the enzymes was carried out by standard methods. Statistical analysis was performed by using Statistica 10 StatSoft Inc. Results. The level of basal glycaemia on the fifth day of the experiment in the animals of both groups went up on average by 115% from baseline values. We founded that on 47-th day this index was higher in group of old rats by 20% than in adult rats. Pyruvate kinase activity in erythrocytes of adult and old animals with diabetes decreased by 35% and 50% respectively compared with the control. Glucose-6-phosphate dehydrogenase activity in erythrocytes of adult and old animals with diabetes decreased by 27% and 45% respectively compared with the control on 47-th day. The changes may be considered as the result of age-related disorders of glucose metabolism due to disturbances in free radical mechanisms. Glutathione reductase activity in erythrocytes of adult and old animals with diabetes decreased by 29% and 35% respectively compared with the control on 47-th day. Conclusion. We have determined when getting aged, the alloxan-diabetic rats demonstrate changes in the sensitivity of pyruvate kinase, glucose-6-phosphate dehydrogenase and glutathione reductase activities in erythrocytes resulted from the effect of diabetes mellitus factors (hyperglycaemia). We can suggest that glycaemic control is key purpose for older patients with type 1 diabetes in order to prevent of complication, which can be aggravated with age.

Key words: blood, alloxan-induced diabetes, aging, rats.

This study is a part of the research project "Stress-induced morphofunctional and biochemical changes in the structures of chronoperiodical and hepatorenal systems in mammals" 0114 U002472 – Fundamental.

Introduction

Diabetes mellitus (DM) is one of the most prevalent endocrine diseases throughout the world. In recent years, a considerably increasing number of people have been found as having DM [4]. The increasing incidence of type 1 diabetes coupled with advances in the treatment of type 1 diabetes has resulted in an unprecedented number of older adult people living with and controllable type 1 diabetes [9].

It is known there are ontogenetic changes in the metabolism of human body [3]. Aging is characterized by a progressive deterioration in physiological functions and metabolic processes. The loss of cells during aging in vital tissues and organs is related to several factors including oxidative stress and inflammation [3].

Oxygen free radicals of mitochondrial origin seem to be involved in aging [12]. Available studies are consistent with the presumption that oxygen radicals endogenously produced by mitochondria

are causally involved in setting the rate of aging in homeothermic vertebrates. Oxidative damage to tissue macromolecules seems to increase during aging. The rate of mitochondrial oxygen radical generation of post-mitotic tissues is negatively correlated with animal longevity.

Hyperglycaemia occurs commonly in acutely and critically ill patients and is associated with adverse clinical consequences. Hyperglycaemia-mediated oxidative stress plays a crucial role in diabetic complications [6].

DM is characterized by metabolic disturbances. The most obvious symptom of diabetes, hyperglycaemia, is caused by inadequate uptake of glucose from the blood. DM manifests itself through hyperglycaemia due to an absolute or relative lack of insulin and/or insulin resistance [1, 2]. A clinical diagnosis of dementia is likely preceded by a period of cognitive decline during which one's ability to properly manage glycaemia may be impacted; this is an especially important limitation in this population of

older adults with type 1 diabetes where self-care plays such an important role in disease management [9].

A researcher Alisdair R Fernie claimed that the respiratory pathways of glycolysis, the tricarboxylic acid (TCA) cycle and the mitochondrial electron transport chain are ubiquitous throughout nature. They are essential for both energy provision in heterotrophic cells and a wide range of other physiological functions.

Glucose-6-phosphate dehydrogenase (insulin-dependent enzyme) is the first enzyme of pentose phosphate pathway. This enzyme accelerates the dehydrogenase reactions in oxidative stage of pentose phosphate pathway, which results in NADPH₂ formation. The cell regenerates reduced glutathione in a reaction catalyzed by glutathione reductase [5, 7].

Ontogenetic shifts in the antioxidant system and carbohydrate metabolism including blood glycolysis against the DM background is less studied.

The objective of this experimental study was to assess the impact of aging on the level of basal glycaemia (BG) and activities of glucose-6-phosphate dehydrogenase (G6PhD, [EC1.1.1.49]), pyruvate kinase (PK, [EC 2.7.1.40]) and glutathione reductase (GR, [EC1.6.4.2]) in erythrocytes of alloxan-induced diabetic rats.

Materials and Methods

The study was carried out in compliance with the Rules for All Vertebrate Animal Studies (1977) and the European Council Convention for the Protection of Vertebrate Animals used in experiments and for other scientific purposes (Strasbourg, 1986), and according to the directions of International Commit-

tee of Medical Journals Editors (ICMJE), as well as to Bioethical expertise of preclinical and other scientific researches conducted on animals (Kyiv, 2006). We used 100 male Wistar rats divided into two age groups: the I group included 2-month (adult) rats, and the II group included 4-month (old) rats. Diabetes was modelled by injecting the rats with 5% solution of alloxan monohydrate intraperitoneally in a dose of 170 mg/kg. Blood was taken from the tail vein to evaluate basal glycaemia (BG) on 5-th and 47-th day after the alloxan injection. The rats were sacrificed on the 47-th day of the experiment in accordance with regulations on the ethical treatment of animals. Assessment of the activity of enzymes was performed by applying standard methods [13]. Statistical analysis was carried out by using Statistica 10 StatSoft Inc. To determine an adequate method of statistical estimation of the average difference between the study groups we used preliminary check of distribution quantities in samples. According to the Shapiro-Wilk test used to assess the normality of distribution in the sample volume $n \leq 50$, all samples, which did not receive data on deviation of the sample distribution from normal ($p > 0.05$). Given these data, the use of Mann-Whitney test was considered sufficient for valid conclusions. Differences were considered to be statistically significant at $p \leq 0.05$.

Results and Discussion

The BG level (fig. 1) on the fifth day of the experiment in the animals of both groups increased on average by 115% from baseline values. We founded that on 47-th day this index was higher in group of old rats by 20% compared with the adult rats.

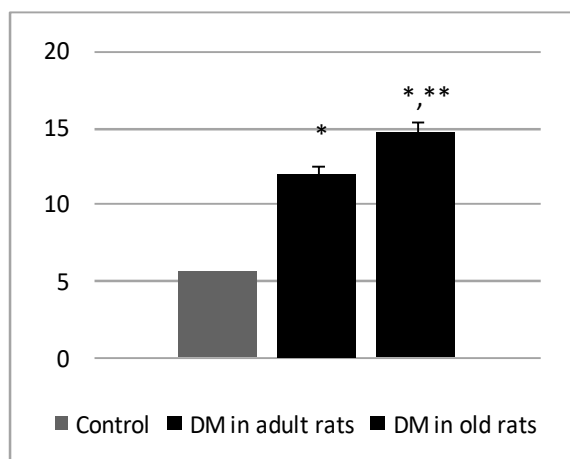


Fig.1. The basal glucose level (mmol/l) in blood of rats, ($n=6$, $\bar{x} \pm Sx$):

1. *, ** - changes are reliable ($p \leq 0.05$).

2. * - concerning control; ** - concerning adult alloxan-induced diabetic rats.

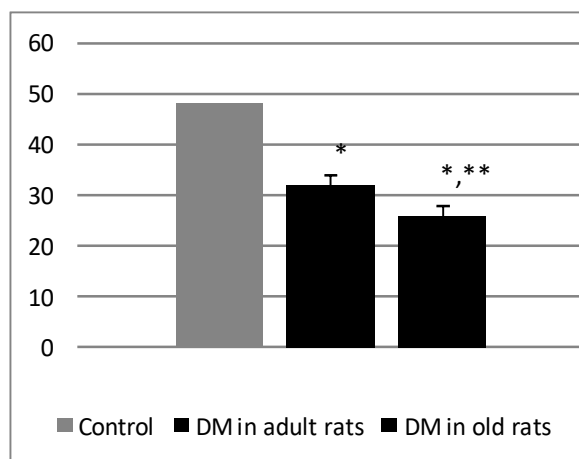


Fig.2. The level of pPyruvate kinase (mkmol/min·g (Hb)) in blood of rats, ($n=6$, $\bar{x} \pm Sx$):

1. *, ** - changes are reliable ($p \leq 0.05$).

2. * - concerning control; ** - concerning adult alloxan-induced diabetic rats.

In our previous studies [6,7] we investigated Langerhans islands in alloxan-diabetic rats and recorded histomorphological alterations: their pancre-

atic share reliably decreased by 55%, number and percentage of beta-cells with necrosis decreased diminished by 90% and 97% respectively compared

with the control.

PK is the enzyme that catalyses the final step of glycolysis. It catalyses the transfer of a phosphate group from phosphoenolpyruvate (PEP) to adenosine diphosphate (ADP), yielding one molecule of pyruvate and one molecule of ATP.

PK activity (fig. 2) in erythrocytes of adult and old animals with diabetes went down by 35% and 50% respectively compared with the control. The tendency toward the decrease in the PK activity can be explained by the fact that PK is regulated by insulin, which is less produced in conditions of alloxan-induced diabetes.

G6PD activity (fig. 3) in erythrocytes of the adult and old animals with diabetes decreased by 27% and 45% respectively compared with the control on 47-th day. This is associated with the reduced NADPH₂ production [8].

GR activity (fig. 4) in erythrocytes of the adult and old animals with alloxan diabetes lowered by 29% and 35% respectively compared with the control on 47-th day.

GR activity (fig. 4) in erythrocytes of the adult and old animals with alloxan diabetes lowered by 29% and 35% respectively compared with the control on 47-th day.

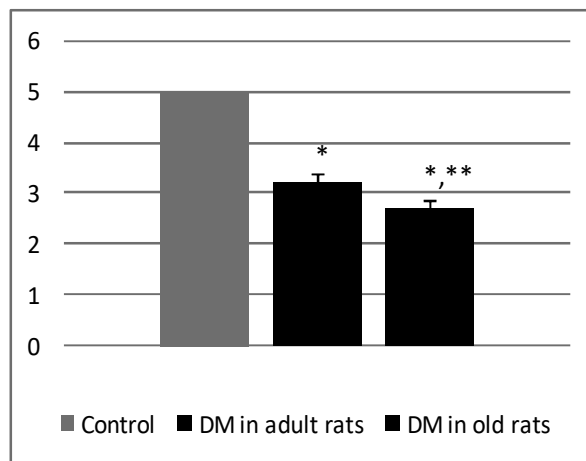


Fig.3. The level of glucose-6-phosphate dehydrogenase (nmol/min-g (Hb)) in blood of rats, (n=6, $\bar{x} \pm Sx$):

1. *, ** - changes are reliable ($p \leq 0.05$).
2. * - concerning control; ** - concerning adult alloxan-induced diabetic rats.

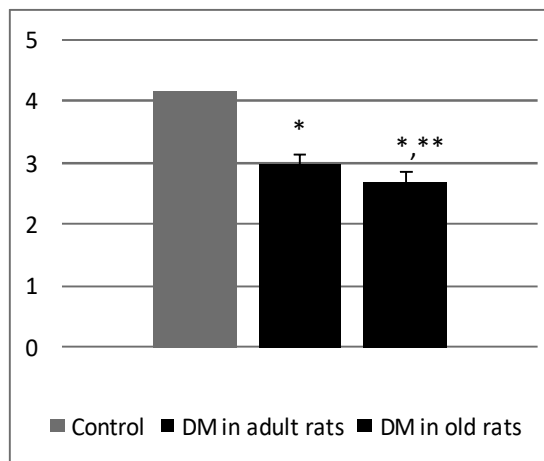


Fig.4. The level of glutathione reductase (mkmol/min-g (Hb)) in blood of rats, (n=6, $\bar{x} \pm Sx$):

1. *, ** - changes are reliable ($p \leq 0.05$).
2. * - concerning control; ** - concerning adult alloxan-induced diabetic rats.

The changes may be explained by age-related disorders of glucose metabolism due to disturbances in free radical mechanisms. Moreover, hyperglycaemia leads to increased free radical mechanism and oxidative modification of protein (insulin and insulin-dependent enzyme) in old rats [11]. Decreased GR activity leads to decline in the reduced glutathione level. These changes may result from age-related disorders of free radical metabolism and age-related NADPH₂ deficiency [9, 10].

Although Yatabe et al. demonstrated somewhat uncertainty they suggest that intermediate blood glucose levels (110–180 mg/dL) may be regarded as the most optimal for adult critically ill patients, with 144–180 mg/dL probably being the preferred target, based on a lower risk of hypoglycaemia than 110–144 mg/dL. Though there have been studies showing a correlation between hypoglycemia and worsened clinical outcomes, a causal link has to be confirmed. Nonetheless, some researchers suggest even mild hypoglycaemia should be avoided in critically ill patients. Since patients who receive insulin infusion are at a higher risk of hypoglycaemia, a reliable tool for measuring blood glucose concentrations, such as an arterial blood gas analyzer, should be frequently used. Acute glycaemic control in patients with premonitory hyperglycaemia is a novel issue.

Conclusion

We have determined when getting aged, the alloxan-diabetic rats demonstrate changes in the sensitivity of pyruvate kinase, glucose-6-phosphate dehydrogenase and glutathione reductase activities in erythrocytes resulted from the effect of diabetes mellitus factors (hyperglycaemia). We can suggest that glycaemic control is key purpose for older patients with type 1 diabetes in order to prevent of complication, which can be aggravated with age factor.

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Реферат

ВІКОВА ЗАЛЕЖНІСТЬ ЗМІН ГЛІКОЛІТИЧНОЇ АКТИВНОСТІ ТА АНТИОКСИДАНТНОГО ЗАХИСТУ В КРОВІ ЩУРІВ З АЛОКСАНОВИМ ДІАБЕТОМ

Кушнір О.Ю., Яремій І.М.

Ключові слова: кров, алоксановий діабет, старіння, щурі.

Зростаюча захворюваність на цукровий діабет 1-го типу в поєднанні з прогресом лікування діабету 1-го типу зумовила безпрецедентну кількість дорослих людей, які живуть та лікують діабет 1-го типу.

Об'єктом цього експериментального дослідження було встановити вплив старіння на рівень базальної глікемії та активності глюкозо-6-фосфатдегідрогенази [EC1.1.1.49], піруваткінази [EC 2.7.1.40] та глутатіонредуктази [EC1.6.4.2] в еритроцитах щурів з алоксановим діабетом. Матеріали та методи. Ми використовували 100 щурів самців Wistar, дві вікові групи: 2-місячний (дорослий) та II - 4-місячний (старий). Алоксановий діабет викликали шляхом ін'єкції щурам 5% розчину алоксану моногідрату внутрішньочеревно з розрахунку 170 мг / кг. Кров відбирали з хвостової вени для оцінки БГ на 5-й і 47-й день після введення алоксану. Декапітацію тварин проводили на 47-й день експерименту відповідно до етичного поводження з тваринами. Визначення активності ферментів проводилось стандартними методами. Статистичний аналіз проводили за допомогою Statistica 10 StatSoft Inc. Результати. Рівень базальної глікемії на п'ятий день експерименту у тварин обох груп в середньому зростав на 115% від значень контролю. Ми встановили, що на 47-й день цей показник був вищим у групі старих щурів на 20% більше, ніж у дорослих щурів. Активність піруваткінази в еритроцитах дорослих і старих тварин з діабетом знизилася на 35% і 50% відповідно порівняно з контролем. Активність глюкозо-6-фосфатдегідрогенази в еритроцитах дорослих та старих тварин із діабетом знизилася на 27% та 45% відповідно порівняно з контролем на 47-й день. Зміни можуть бути наслідком вікових порушень метаболізму глюкози через порушення механізмів вільних радикалів. Активність глутатіонредуктази в еритроцитах дорослих та старих тварин із діабетом зменшилась на 29% та 35% відповідно порівняно з контролем на 47-й день. Висновок. Ми встановили, що в ході старіння відбулися зміни чутливості активностей піруваткінази, глюкозо-6-фосфатдегідрогенази та глутатіонредуктази в еритроцитах щурів з алоксановим діабетом до впливу діабетичного статусу (гіперглікемія). Ми висунули гіпотезу, що контроль глікемії є цільовим призначенням для літніх пацієнтів з діабетом 1 типу для запобігання ускладнень, пов'язаних зі старінням організму.

Реферат

ВОЗРАСТНАЯ ЗАВИСИМОСТЬ ИЗМЕНЕНИЯ ГЛИКОЛИТИЧЕСКОЙ АКТИВНОСТИ И АНТИОКСИДАНТНОЙ ЗАЩИТЫ В КРОВИ КРЫС С АЛЛОКСАНОВЫМ ДИАБЕТОМ

Кушнір А.Ю., Яремий И.М.

Ключевые слова: кровь, аллоксановый диабет, старение, крысы.

Растущая заболеваемость сахарным диабетом 1-го типа в сочетании с прогрессом лечения диабета 1-го типа обуславливает беспрецедентное количество взрослых людей, которые живут и лечат диабет 1-го типа. Объектом этого экспериментального исследования было установить влияние старения на уровень базальной гликемии и активность глюкозо-6-фосфатдегидрогеназы [EC1.1.1.49], пируваткиназы [EC 2.7.1.40] и глутатионредуктазы [EC1.6.4.2] в эритроцитах крыс с аллоксановым диабетом.

Материалы и методы. Мы использовали 100 крыс самцов Wistar, две возрастные группы: 2-месячный (взрослый) и II - 4-месячный (старый). Аллоксановый диабет вызвали путем инъекции крысам 5% раствора аллоксана моногидрата внутривентрально из расчета 170 мг / кг. Кровь отбирали из хвостовой вены для оценки базальной гликемии на 5-й и 47-й день после введения аллоксана. Декапитацию животных проводили на 47-й день эксперимента в соответствии с принципами этического обращения с животными. Определение активности ферментов проводилось стандартными методами. Статистический анализ проводили с помощью Statistica 10 StatSoft Inc. Результаты. Уровень базальной гликемии на пятый день эксперимента у животных обеих групп вырос в среднем на 115% от значений контроля. Мы установили, что на 47-й день этот показатель был выше в группе старых крыс на 20% больше, чем у взрослых крыс. Активность пируваткиназы в эритроцитах взрослых и старых жи-

вотных с диабетом снизилась на 35% и 50% соответственно по сравнению с контролем. Активность глюкозо-6-фосфатдегидрогеназы в эритроцитах взрослых и старых животных с диабетом снизилась на 27% и 45% соответственно по сравнению с контролем на 47-й день. Изменения могут быть следствием возрастных нарушений метаболизма глюкозы из-за нарушения механизмов свободных радикалов. Активность глутатионредуктазы в эритроцитах взрослых и старых животных с диабетом уменьшилась на 29% и 35% соответственно по сравнению с контролем на 47-й день. Вывод. Мы установили, что в ходе старения произошли изменения чувствительности активностей пируваткиназы, глюкозо-6-фосфатдегидрогеназы и глутатионредуктазы в эритроцитах крыс с аллоксановым диабетом к влиянию диабетического статуса (гипергликемия). Мы выдвинули гипотезу, что контроль гликемии является целевым назначением для пожилых пациентов с диабетом 1 типа для предотвращения осложнений, связанных со старением организма.

DOI 10.31718/2077-1096.20.3.173

UDC: 616.345-006.5+616.345-006.6]-074:577.112]-042.2

Shyshkin M.A.

COMPARATIVE ANALYSIS OF CD44 EXPRESSION IN POLYPS AND ADENOCARCINOMA OF DISTAL COLON

Zaporizhzhia State Medical University

Introduction. CD44 is one of the most used markers of cancer stem cells in colorectal cancer. Even though, the questions of its diagnostic and prognostic value remain open. The aim of the study was to compare CD44 immunohistochemical expression levels in polyps and adenocarcinoma of the distal colon. Materials and methods. Histopathological and immunohistochemical studies of biopsies from 40 patients and surgical material of colorectal adenocarcinoma from 30 patients were carried out. Results. It was figured out that distal colonic polyps are characterized by membranous CD44 expression with the medians of relative areas of CD44+ cells equal to 60,24 (50,22; 70,22) % stromal cells and 15,67 (12,47; 19,47) % epitheliocytes. Colorectal adenocarcinoma is characterized by membranous-cytoplasmic CD44 expression with the medians of relative areas of CD44+ cells equal to 61,26 (42,58 ; 79,15) % stromal cells and 30,60 (24,56 ; 36,45) % cancer cells. Comparative analysis of the data obtained for the pTNM stages of colorectal adenocarcinoma revealed some significant differences. The median of CD44+ stromal cells area on the I stage equals to 31,41 (19,87 ; 42,15) % vs. the median of CD44+ stromal cells area on the II stage equals to 48,26 (35,44 ; 61,45) % , $p < 0,05$; the median of CD44+ stromal cells area on the II stage vs. the median of CD44+ stromal cells area on the III stage equals to 78,36 (61,13 ; 80,06) % , $p < 0,05$. The median of CD44+ cancer cells area on the III stage equals to 30,35 (21,19 ; 35,47) % vs. the median of CD44+ cancer cells area on the IV stage equals to 31,25 (30,22 ; 41,19) % , $p < 0,05$. Moreover, it was revealed that the median of CD44+ epitheliocytes area in polyps two-fold smaller than the median of CD44+ cancer cells area in colorectal adenocarcinoma: 15,67 (12,47 ; 19,47) % vs. 30,60 (24,56 ; 36,45) % , $p < 0,05$. Conclusions. Distal colonic polyps are characterized by membranous CD44 expression with the median of CD44+ epitheliocytes area that is two-fold smaller than the median of CD44+ cancer cells area. Colorectal adenocarcinoma is characterized by membranous-cytoplasmic CD44 expression with the median of CD44+ stromal cells area that significantly increases during the tumor progression from I to III stages and with the median of CD44+ cancer cells area that significantly go up during the tumor progression from III to IV stages.

Key words: polyps, colorectal cancer, CD44 antigen.

The research is funded as a part of planned research project "Comorbidity, cardiovascular and oncological diseases in general clinical practice: development of modern diagnostic and therapeutic measures" in Zaporizhzhia State Medical University, number of state registration 0120U101587 (2020-2023).

Annually, approximately 1.3 million new cases of colorectal cancer (CRC) are diagnosed worldwide [1]. The CRC development is preceded by an abnormal proliferation of the colonic mucosa that forms a polyp in most cases. The excessive proliferation is considered to be a result of a combination of unfavourable external factors (smoking, alcohol abuse, lack of plant fibre in the diet) and genetic predisposition, which through molecular-genetic modifications can trigger the "polyp-carcinoma" se-

quence [2].

During the last decade, a significant amount of data regarding cancer stem cells (CSCs) subpopulation and their role in tumour initiation and progression has been accumulated [3-5]. CD44 is one of the most used markers of CSCs in CRC. Even though, the questions of its diagnostic and prognostic value for CRC patients are still remaining open [4].

CD44 is a transmembrane glycoprotein that is expressed by embryonic stem cells, as well as by some progenitor and mature cells, including cells of connective tissue and bone marrow [6]. According to the literature, the CD44 gene is a part of an intestinal stem cell gene signature [7]. In addition, it is known that CD44 expression is characteristic of the CSCs subpopulation [8]. The main ligand of CD44