УДК 577.171.5:612.826.33.015.22:612.121
DOI 10.11603/mcch.2410-681X.2018.v0.i4.9781

N. M. Luhinich, I. V. Gerush, N. P. Grygorieva
BUKOVYNA STATE MEDICAL UNIVERSITY, CHERNIVTSI

EFFECTS OF MELATONIN ON OXIDANT AND ANTIOXIDANT STATUS IN THE BLOOD OF ALLOXAN DIABETIC RATS

Introduction. *The experimental model of alloxan diabetes is quite common, which is often used to study the different aspects of pathogenesis and pathomorphology of diabetes. It is known that during the diabetes activation of free radical oxidation of biomolecules occurs as well as depletion of the antioxidant system. Melatonin can suppress reactive oxygen species and increases the activity of antioxidant enzymes.*

The aim of the study *– to investigate the effect of melatonin on oxidant and antioxidant status in the blood of alloxan diabetic rats.*

Research Methods. *Experiments were conducted on white outbred sexually mature male rats. In the blood plasma was determined content of oxidatively modified proteins, the ceruloplasmin activity; in the hemolisate of erythrocytes was determined content of TBA-reactive products, the measurement of superoxide dismutase (SOD) and catalase activities.*

Results and Discussion. *The results of our studies showed that under conditions of alloxan diabetes, processes of free radical damage to biomolecules are intensified, as evidenced by the increase in the content of TBA-active products and oxidatively modified proteins in the blood of rats on 7 and 14 days of alloxan diabetes. The activity of catalase and ceruloplasmin in the blood of alloxan diabetic rats was lower than in the control group of animals but the SOD activity was significantly increased. The positive effect of melatonin is shown on 7 and 14 days and decrease the content of TBA-active products and oxidatively modified proteins blood of rats compared with untreated animals. Also, the administration of melatonin contributed to the normalization of the activity antioxidant enzymes of blood in rats with alloxan diabetes: increase of catalase activity in erythrocytes, ceruloplasmin activity and decrease SOD activity compared with untreated animals.*

Conclusion. *The introduction of exogenous melatonin in rats with alloxan diabetes in a dose of 10 mg/kg daily for 7 and 14 days cause a pronounced antioxidant effect, reducing free radical oxidation and normalizing the activity of enzymes of antioxidant defense in the blood alloxan diabetic rats.*

KEY WORDS: **diabetes mellitus; melatonin; alloxan; blood; oxidative stress; antioxidant system.**

INTRODUCTION. The most relevant problems of modern medicine is the search for means to improve the therapy of diabetes, which has become widespread in last years due to the progress of many amplifications of this disease.

Complications of diabetes include cardiovascular disease, chronic renal insufficiency and diabetes retinopathy. These complications associated with hyperglycemia cause oxidative stress in the body [1].

The experimental model of alloxane diabetes is quite common, which is often used to study the different aspects of pathogenesis and pathomorphology of diabetes [2]. It is known that during the diabetes activation of free radical oxidation of biomolecules occurs as well as depletion of the antioxidant system [3].

Free radicals formed at oxidative stress are highly toxic to cellular components especially lipids and proteins that are part of cell membranes. Free radicals destroy lipids and proteins on the membranes and cause modifications and oxidation of lipids and proteins thereby damaging cells. Lipid and protein oxidation products is metabolized by non-enzymatic and enzymatic mechanisms to eliminate oxidative stress [3].

Melatonin (5-methoxy-N-acetyltriptamine) is one of the strongest antioxidants that is secreted by the daily rhythm of the pineal gland [4].

Recently, scientists and physicians actively studied the physiological effects of melatonin on different organs and systems, as this hormone has somnogenic effect and it is a regulator of circadian systems of the organism as well as the immune system stimulator and shows protective properties from premature senescence, cancer, stress and is an antioxidant. It can suppresses reactive oxygen species (ROS) and increases the activity of antioxidant enzymes [3].

It is believed that melatonin may be useful for therapy many diseases, such as depression, insomnia, obesity, cancer, and immune and cardiac disorders. [3, 5]. This study was aimed to investigate the effect of melatonin on oxidant and antioxidant status in the blood of alloxan diabetic rats.

RESEARCH METHODS. The experiments were carried out on sexually mature male albino rats with the body weight – 150–160 g. These animals were housed in polypropylene cages under standard environmental conditions of temperature, relative humidity, and dark/light cycle. Animals described as fasted were deprived of food and water for 16 hours ad libitum. Animal keeping, handling and manipulating were in accordance with the First National Congress of Bioethics of Ukraine (Kyiv, 2001), "European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes" (Strasbourg, 1986) and with regard to NIH Guide for the Care and Use of Laboratory Animals (Washington, DC: National Academies Press, 2011).

Alloxan diabetes was evoked via single injecting the rats with 5 % alloxan monohydrate solution (Sigma Chemicals Company: 150 mg/kg body weight) dissolved in normal saline to the male rats, after an overnight fast (access to only water) of 12 hours to make them more susceptible to developing diabetes [6]. Another group of rats (control) were injected with the same volume of normal saline. After 72 h the injection of alloxan monohydrate, fasting blood glucose concentration was measured with a Longevita glucometer (Network Selects LTD, Great Britain) using blood samples from the tip of the tail. Animals with blood glucose concentrations ≥15.2 mmol/L were considered diabetic and used in this study.

After diabetes induction, melatonin (10 mg/kg daily) was administered by intragastrically to the animals in the melatonin-treated group, for 7 or 14 days.

The animals were divided into the next groups: control rats – group I; diabetes (7 days) – group II; diabetes+melatonin (7 days) – group III; diabetes (14 days) – group IV; diabetes+melatonin (14 days) – group V.

In the blood of rats that was received by decapitation under light ether anesthesia, 24 hours after the last dose of the melatonin was determined glucose by the glucose oxidase method using standard analytical kit "Filisit-Diagnosis" (Ukraine). In the blood plasma was determined content of oxidatively modified proteins [7], the ceruloplasminactivity [8]; in the hemolisate of erythrocytes was determined content of TBA-reactive products [9], the measurement of superoxide dismutase (SOD) [10] and catalase activities [11].

All data are expressed as means±S.E. and represent at least four independent experiments. Significant differences between groups were evaluated by using Wilcoxon test with $p<0.05$.

RESULTS AND DISCUSSION. During the experiment, an increased level of glucose in the blood was found what is typical for diabetes mellitus.

It was established that under conditions of alloxan diabetes, processes of free radical damage to biomolecules are intensified, as evidenced by the increase in the content of TBA-active products in the blood by 21 % in 7 days of alloxan diabetes (Figure 1). At the 14th day of diabetes, the content of TBA-active products increased by 31 %, that indicating the increase of oxidative stress.

Oxidative modification and destruction of proteins is one of the earliest and most important indicators of tissue damage at free radicals pathology [12]. We explored that at the 7th day of the experiment occurs the increase of the content of oxidatively modified proteins in blood plasma of alloxan diabetic rats on 18 % higher than the control level as well as on the 14th day of alloxan diabetes the content of oxidatively modified proteins increased on 12 % (Figure 2).

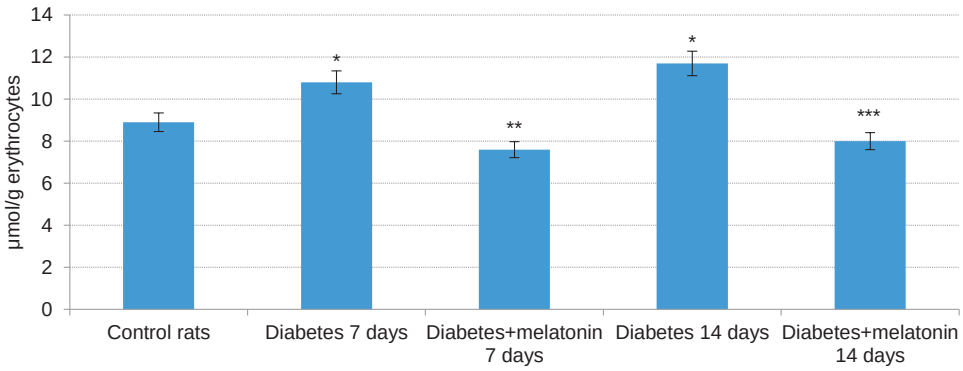

Fig. 1. Effect of melatonin introduction on the TBA-product in the blood.

Note. Values are statistically significant: * – $p<0.05$ compared with control group; ** – $p<0.05$, compared with diabetic group after 7 days; *** – $p<0.05$, compared with diabetic group after 14 days.

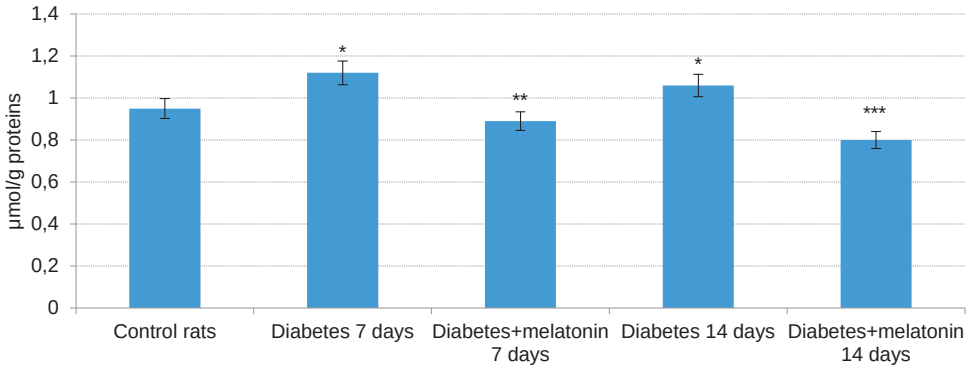

Fig. 2. Effect of melatonin introduction on the content of oxidatively modified proteins in the blood.

Note. Values are statistically significant: * – p<0.05 compared with control group; ** – p<0.05, compared with diabetic group after 7 days; *** – p<0.05, compared with diabetic group after 14 days.

We found that the introduction of melatonin to rats with alloxan diabetes daily for 7 days contributed to a decrease the content of TBA-active products in rats erythrocytes on 46 % and the content of oxidatively modified proteins in blood plasma of rats on 21 % in comparison with untreated animals.

The positive effect of melatonin is shown on 14 days and decrease the content of TBA-active products on 32 % in rats erythrocytes and the content of oxidatively modified proteins on 25 % in blood plasma of rats compared with untreated animals.

Important indicators of the develop of free radical reactions are the activity enzymes of antioxidant defense and one the most important enzyme is catalase.

The activity of catalase decrease by 13 % below the control level at 7 days in the blood of alloxan diabetic rats. On the 14th day of the experiment there is a similar trend – a decrease on 11 % (Table).

In alloxan diabetic rats we recorded a significant increase SOD activity on 33 % at 7 days and 34 % at 14 days in blood compared to animals in the control group.

Growing SOD activity may be due to an increase concentration of hydrogen peroxide in the cells and inactivation of enzymes that it splitting, in particular catalase. This confirms the decrease activity of catalase in the blood of alloxan diabetic rats compared with animals in the control group.

The activity of ceruloplasmin in blood plasma of rats with alloxane diabetes is lower than in the control group of animals for 7 and 14 days by 38 % and 29 % respectively. Therefore, the level of activity detected in the experiment may be due to the depletion of the antioxidant defense system. As a result, evoked oxidative stress, which break the pro- and antioxidant balance.

The introduction of melatonin during 7 days also contributed to the normalization of the activity of antioxidant blood enzymes in rats with alloxane diabetes: the catalase and ceruloplasmin activities was higher on 23 % and 20 % respectively and decrease SOD activity on 26 % compared with alloxan diabetic rats.

Also, the administration of melatonin during 14 days contributed to the normalization of the activity antioxidant enzymes of blood in rats with alloxan diabetes: increase of catalase activity on 13 % in erythrocytes, ceruloplasmin activity on 20 % and decrease SOD activity on 27 % compared with untreated animals.

Evidence an effective antioxidant effect is a significant decrease glucose levels in blood of treated rats compared with alloxan diabetic group at 7 days (56 %, p<0.05) and 14 days (55 %, p<0.05) of the experiment.

Table – **Effects of melatonin on antioxidant status in the blood of alloxan diabetic rats**

Group	Controls, n=39	Diabetes (7 days), n=18	Diabetes+ Melatonin (7 days), n=19	Diabetes (14 days), n=19	Diabetes+ Melatonin (14 days), n=18
Catalase, µmol/min·L blood	10.95±0.38	9.51±0.53*	11.7±0.68**	9.73±0.27*	11.03±0.51***
SOD, U/g HB	1.84±0.08	2.44±0.21*	1.81±0.07**	2.46±0.27*	1.79±0.09***
Ceruloplasmin, mg/L serum	254.86±10.16	157.91±13.85*	189.60±12.90**	180.76±9.78*	216.19±11.68***

Note. Values are statistically significant: * – p<0.05 compared with control group; ** – p<0.05, compared with diabetic group after 7 days; *** – p<0.05, compared with diabetic group after 14 days.

The obtained results evidence to the effectiveness of the use of melatonin for the correction of the antioxidant defense system in experimental diabetes mellitus. The antidiabetic melatonin function implemented at the cellular and systemic levels [5]. An important aspect of the cellular effect of melatonin is its effect on the process of lipid peroxidation and the level of free radicals that grow in diabetes mellitus [13].

Antioxidant effect of melatonin is likely related to the ability to intercept free radicals due to the presence in its composition indole ring [13]. Also known data that melatonin may directly effect of genes expression responsible for the synthesis of antioxidant enzymes [14].

The results of our studies confirm the existence of protective, antioxidant, anti-diabetic properties in melatonin. As a result of the study is detected obvious participation of melatonin in the regulation of glucose metabolism and its contribution to the pathogenesis of diabetes mellitus.

CONCLUSIONS. We found that alloxan diabetes was observed by an increase the content of TBA-active products and oxidatively modified proteins and SOD activity in the blood on the background of a significant increase the blood glucose levels in rats and reduced activity of catalase, and ceruloplasmin. In conditions of alloxane diabetes and the introduction of exogenous melatonin in rats with alloxan diabetes in a dose of 10 mg/kg daily for 7 and especially 14 days, it caused a pronounced antioxidant effect, lowering free radical oxidation and normalizing the activity of enzymes of antioxidant defense in the blood alloxan diabetic rats.

LITERATURE

1. Dal S. The protective effect of antioxidants consumption on diabetes and vascular complications [Electronic resource] / S. Dal, S. Sigrist // Diseases. – 2016. – **4**. – P. 24. – Mode access : https://doi:10.3390/diseases4030024.

2. Antidiabetic activity of differently regioselective chitosan sulfates in alloxan-induced diabetic rats / R. Xing, X. He, S. Liu [et al.] // Marine Drugs. – 2015. – **13**. – P. 3072–3090.

3. Effect of melatonin versus vitamin D as antioxidant and hepatoprotective agents in STZ-induced diabetic rats / A. A. Alqasim, E. M. Noureldin,S. H. Hammadi, G. E. Esheba // Journal of Diabetes & Metabolic Disorders. – 2017. – **29**. – P. 16–41.

4. Oxidative modification of blood serum proteins in multiple sclerosis after interferon beta and melatonin treatment [Electronic resource] / M. Adamczyk-Sowa, S. Galiniak, E. Żyracka [et al.] // Oxidative Medicine and Cellular Longevity. – 2017. – Article ID 7905148 – P. 8. – Mode access: https://doi.org/10.1155/2017/7905148.

5. Transcutaneous vagus nerve stimulation induces tidal melatonin secretion and has an antidiabetic effect in zucker fatty rats [Electronic resource] / S. Wang, X. Zhai, S. Li [et al.] // Plos One. – 2015. – No. 16. – P. 12. – Mode access : https://doi:10.1371/journal.pone.0124195.

6. Akinola O. Treatment of alloxan-induced diabetic rats with metformin or glitazones is associated with amelioration of hyperglycaemia and neuroprotection / O. Akinola, M. Gabriel, A. Suleiman // The Open Diabetes Journal. – **5**. – P. 8–12.

7. Мещишен І. Ф. Метод визначення окисномодифікованих білків плазми (сироватки) крові / І. Ф. Мещишен // Буковин. мед. вісн. – 1998. – **2**, № 1. – С. 156–158.

8. Колб В. Г. Справочник по клинической химии / В. Г. Колб, В. С. Камышников. – Минск : Беларусь, 1982. – 290 с.

9. Камышников В. С. Справочник по клинико-биохимической лабораторной диагностике / В. С. Камышников. – Минск : Беларусь, 2002. – 494 с.

10. Окислительная модификация белков сыворотки крови человека, метод ее определения / Е. Е. Дубинина, С. О. Бурмистров, Д. А. Ходов [и др.] // Вопр. мед. химии. – 1995. – № 1. – С. 24–26.

11. Метод определения активности каталазы / К. А. Королюк, Л. И. Иванова, И. Г. Майорова [и др.] // Лаб. дело. – 1988. – № 1. – С. 16–19.

12. Дубинина Е. Е. Окислительная модификация протеинов, ее роль при патологических состояниях / Е. Е. Дубинина, А. В. Пустыгина // Укр. біохім. журн. – 2008. – **80**, № 6. – С. 5–18.

13. Melatonin decreases glucose metabolism in prostate cancer cells: a 13c stable isotope-resolved metabolomic study [Електронний ресурс] / D. Hevia, P. Gonzalez-Menendez, M. Fernandez-Fernandez [et al.] // International Journal of Molecular Sciences. – 2017. – **18** – P. 8. – Mode access : https://doi:10.3390/ijms18081620.

14. Melatonin as a therapeutic resource for inflammatory visual diseases rosenstein / M. L. Aranda, M. F. González Fleitas, H. Dieguez [et al.] // Current Neuropharmacology. – 2017. – **15**. – P. 951–962.

REFERENCES

1. Dal, S.,& Sigrist S.(2016).The protective effect of antioxidants consumption on diabetes and vascular complications. *Diseases*, 4, 24. doi:10.3390/diseases4030024.

2. Xing, R., He, X., Liu, S., Yu, H., Qin, Y., Chen X., & Li, K.(2015).Antidiabetic activity of differently regioselective chitosan sulfates in alloxan-induced diabetic rats. *Marine Drugs*, 13, 3072–3090. doi:10.3390/md13053072.

3. Alqasim, A.A., Noureldin, E.M., Hammadi, S.H., & Esheba,G.E. (2017). Effect of melatonin versus vitamin D as antioxidant and Hepatoprotective agents in STZ-induced diabetic rats. *Journal of Diabetes & Metabolic Disorders*, 29, 16-41.doi 10.1186/s40200-017-0322-6.

4. Adamczyk-Sowa, M., Galiniak, S., Żyracka, E., Grzesik, M., Naparło, K., Sowa, P., Bartosz, G., & Sadowska-Bartosz, I. (2017). Oxidative modification of blood serum proteins in multiple sclerosis after interferon beta and melatonin treatment. *Oxidative Medicine and Cellular Longevity*, 8.doi.org/10.1155/2017/7905148.

5. Wang, S., Zhai, X., Li, S., Cabe, M. F., Wang, X., & Rong, P. (2015).Transcutaneous vagus nerve stimulation induces tidal melatonin secretion and has an antidiabetic effect in zucker fatty rats. *Plos One*, 16, 12. doi: 10.1371/journal.pone.0124195.

6. Akinola O., Gabriel M., & Suleiman A. (2012). Treatment of alloxan-induced diabetic rats with metformin or glitazones is associated with amelioration of hyperglycaemia and neuroprotection. *The Open Diabetes Journal*, 5, 8-12.

7. Meshchyshen, I.F. (1998). Metod vyznachennia okysno modyfikovanykh bilkiv plazmy (syrovatky) krovi [Method for the determination of oxidative plasma blood (serum) proteins]. *Bukovynskyi medychnyi visnyk – Bukovyna Medical Herald, 2,* (1), 156-158 [in Ukrainian].

8. Kolb, V.G., & Kamyshnikov, V.S. (1982). *Spravochnik po klinicheskoy khimii [Reference book on Clinical Chemistry].* Minsk [in Russian].

9. Kamyshnikov, V.S. (2002). *Spravochnik po klinikobiokhimicheskoy laboratornoy diagnostike (2-e izd.) [Reference book on Clinical Chemistry (2-nd ed.)].* Minsk [in Russian].

10. Dubinina, E.E., Burmistrov, S.O., & Khodov, D.A. (1995). Okislitelnaya modifikatsiya belkov syrovotki krovi cheloveka, metod ee opredeleniya [Oxidative modification of human serum proteins, method of its determination]. *Voprosy meditsinskoy khimii – Issues of Medical Chemistry, 41,* 24-26 [in Russian].

11. Korolyuk, K.A., Ivanova, L.I., & Mayorova, I.G. (1988). Metod opredeleniya aktivnosti katalazy [Method for the determination of catalase activity]. *Laboratornoye delo – Laboratory Business, 1,* 16-19 [in Russian].

12. Dubinina, E.E., & Pustygina, A.V. (2008). Okislitelnaya modifikatsiya proteinov, ee rol pri patologicheskikh sostoyaniyakh [Oxidative modification of proteins, its role in pathological conditions]. *Ukrainskyi biokhimichnyi zhurnal – Ukrainian Biochemical Journal*, 6, 5-18 [in Russian].

13. Hevia, D., Gonzalez-Menendez, P., & Fernandez-Fernandez, M. (2017). Melatonin decreases glucose metabolism in prostate cancer cells: a 13c stable isotope-resolved metabolomics study. *International Journal of Molecular Sciences*, 18. doi:10.3390/ijms18081620.

14. Aranda, M.L., González Fleitas, M.F., Dieguez, H., Iaquinandi, A., Sande, P.H., Ruth, D.D. (2017). Melatonin as a therapeutic resource for inflammatory visual diseases rosenstein. *Current Neuropharmacology*, 15, 951-962.

Н. М. Лугініч, І. В. Геруш, Н. П. Григор'єва
БУКОВИНСЬКИЙ ДЕРЖАВНИЙ МЕДИЧНИЙ УНІВЕРСИТЕТ, ЧЕРНІВЦІ

ВПЛИВ МЕЛАТОНІНУ НА ОКСИДАНТНИЙ ТА АНТИОКСИДАНТНИЙ СТАТУС КРОВІ В АЛОКСАНДІАБЕТИЧНИХ ЩУРІВ

Резюме

Вступ. *Експериментальна модель алоксанового цукрового діабету є досить поширеною, її часто використовують для вивчення різних аспектів патогенезу та патоморфології діабету. Відомо, що при цукровому діабеті відбувається активація вільнорадикального окиснення біомолекул, а також виснаження антиоксидантної системи. Мелатонін може знешкоджувати активні форми кисню та підвищувати активність антиоксидантних ферментів.*

Мета дослідження *– вивчити вплив мелатоніну на оксидантний та антиоксидантний статус крові в алоксандіабетичних щурів.*

Методи дослідження. *Досліди проведено на білих безпородних статевозрілих щурах-самцях. У плазмі крові визначали вміст окисномодифікованих білків, активність церулоплазміну, в гемолізаті еритроцитів – вміст ТБК-активних продуктів, активність супероксиддисмутази і каталази.*

Результати й обговорення. *Результати наших досліджень показали, що за умов алоксанового цукрового діабету посилювалися процеси вільнорадикальних ушкоджень біомолекул, про що свідчило збільшення на 7-й та 14-й дні експерименту вмісту ТБК-активних продуктів та окисномодифікованих білків у крові алоксандіабетичних щурів. Водночас спостерігали зниження активності каталази, церулоплазміну і зростання активності супероксиддисмутази у крові тварин діабетичної групи. Введення мелатоніну*

мало позитивний ефект як на 7-й, так і на 14-й дні експерименту, що проявлялося зменшенням вмісту ТБК-активних продуктів і окисномодифікованих білків у крові щурів порівняно з алоксандіабетичними тваринами. Крім того, застосування мелатоніну сприяло нормалізації активності антиоксидантних ферментів у крові щурів з алоксановим цукровим діабетом: підвищенню активності каталази і церулоплазміну на фоні зниження активності супероксиддисмутази порівняно з алоксандіабетичними тваринами.

***Висновок.** За умов алоксанового цукрового діабету і введення щурам екзогенного мелатоніну в дозі 10 мг/кг щоденно впродовж 7-ми та 14-ти днів спостерігають зменшення вільнорадикального окиснення та нормалізацію активності ферментів антиоксидантного захисту в крові алоксандіабетичних тварин.*

КЛЮЧОВІ СЛОВА: **цукровий діабет; мелатонін; алоксан; глутатіон; антиоксидантна система.**

Н. М. Лугинич, И. В. Геруш, Н. Ф. Григорьева
БУКОВИНСКИЙ ГОСУДАРСТВЕННЫЙ МЕДИЦИНСКИЙ УНИВЕРСИТЕТ, ЧЕРНОВЦЫ

ВЛИЯНИЕ МЕЛАТОНИНА НА ОКСИДАНТНЫЙ И АНТИОКСИДАНТНЫЙ СТАТУС КРОВИ В АЛЛОКСАНДИАБЕТИЧЕСКИХ КРЫС

Резюме

***Вступление.** Экспериментальная модель аллоксанового сахарного диабета является довольно распространенной, ее часто используют для изучения различных аспектов патогенеза и патоморфологии диабета. Известно, что при сахарном диабете происходит активация свободнорадикального окисления биомолекул, а также истощение антиоксидантной системы. Мелатонин может обезвреживать активные формы кислорода и повышать активность антиоксидантных ферментов.*

***Цель исследования** – изучить влияние мелатонина на оксидантный и антиоксидантный статус крови в аллоксандиабетических крыс.*

***Методы исследования.** Опыты проведены на белых беспородных половозрелых крысах-самцах. В плазме крови определяли содержание окислительномодифицированных белков, активность церулоплазмина, в гемолизате эритроцитов – содержание ТБК-активных продуктов, активность супероксиддисмутазы и каталазы.*

***Результаты и обсуждение.** Результаты наших исследований показали, что в условиях аллоксанового сахарного диабета усиливались процессы свободнорадикальных повреждений биомолекул, о чем свидетельствовало увеличение на 7-й и 14-й дни эксперимента содержания ТБК-активных продуктов и окислительномодифицированных белков в крови аллоксандиабетических крыс. Наряду с этим наблюдали снижение активности каталазы, церулоплазмина и возрастание активности супероксиддисмутазы в крови животных диабетической группы. Введение мелатонина имело положительный эффект как на 7-й, так и на 14-й дни эксперимента, что проявлялось уменьшением содержания ТБК-активных продуктов и окислительномодифицированных белков в крови крыс по сравнению с аллоксандиабетическими животными. Кроме того, применение мелатонина способствовало нормализации активности антиоксидантных ферментов в крови крыс с аллоксановым сахарным диабетом: повышению активности каталазы и церулоплазмина на фоне снижения активности супероксиддисмутазы по сравнению с аллоксандиабетическими животными.*

***Вывод.** В условиях аллоксанового сахарного диабета и введения крысам экзогенного мелатонина в дозе 10 мг/кг ежедневно в течение 7-ми и 14-ти дней наблюдают уменьшение свободнорадикального окисления и нормализацию активности ферментов антиоксидантной защиты в крови аллоксандиабетических животных.*

КЛЮЧЕВЫЕ СЛОВА: **сахарный диабет; мелатонин; аллоксан; глутатион; антиоксидантная система.**

Received 07.11.18

Address for correspondence: *N. M. Luhinich, Bukovyna State Medical University, Teatralna Street. 2, Chernivtsi, 58002, Ukraine, e-mail: nlevytska@ukr.net.*