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EXPERIMENTAL SUBSTANTIATION OF THE EXPEDIENCY OF THE COMBINED USE OF PIRACETAM AND METFORMIN FOR PHARMACOLOGICAL CORRECTION OF COGNITIVE DISORDERS IN CONDITIONS OF PROLONGED HYPERGLYCEMIA

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Ключові слова: *алоксан-індукована гіперглікемія, діабетична енцефалопатія, когнітивний дефіцит, метформін, пірацетам*
Ключевые слова: *аллоксан-индуцированная гипергликемия, диабетическая энцефалопатия, когнитивный дефицит, метформин, пирацетам*

Abstract. Experimental substantiation of the expediency of the combined use of piracetam and metformin for pharmacological correction of cognitive disorders in conditions of prolonged hyperglycemia. Lievykh A.E., Bondarenko N.S., Dronov S.N., Mamchur V.I., Tverdokhlib I.V., Zhyliuk V.I. *Chronic hyperglycemia, insulin resistance, endothelial dysfunction, and disturbance of the integrity of the blood-brain barrier are considered as strategically important links in the development of cognitive deficits in diabetic encephalopathy. Taking this into account, one of the modern trends in the optimization of the treatment of cognitive impairments induced by prolonged hyperglycemia is the co-administration of agents with antihyperglycemic and nootropic activity, in particular, metformin with piracetam. It has been shown that under conditions of experimental alloxan-induced hyperglycemia, piracetam has insufficient nootropic potential for eliminating cognitive deficits. Metformin has a weak nootropic effect in short-term use in low doses, without exhibiting these properties in prolonged administration. When combined with piracetam, metformin potentiates its antiamnesic properties, which helps to restore cognitive functions impaired by hyperglycemia. It is assumed that the mechanisms of such synergism are mediated by a decrease in the content of early and late markers of the destruction of protein molecules, the level of stable nitric oxide metabolites in the cerebral cortex, as well as a significant limitation of the manifestations of ultrastructural destructive changes in hippocampal neurons with a simultaneous improvement in the state of its microvasculature. The obtained results indicate the expediency of the combined use of metformin with nootropic agents for the prevention or treatment of cognitive impairments that occur as a result of diabetes mellitus.*

Реферат. Экспериментальное обоснование целесообразности сочетанного применения пирацетама и метформина для фармакологической коррекции когнитивных расстройств в условиях длительной гипергликемии. Левых А.Э., Бондаренко Н.С., Дронов С.Н., Мамчур В.И., Твердохлеб И.В., Жилюк В.И. *Стратегически важными звеньями развития когнитивного дефицита при диабетической энцефалопатии считают хроническую гипергликемию, инсулинорезистентность, эндотелиальную дисфункцию и нарушение целостности гематоэнцефалического барьера. С учетом этого, одним из современных трендов оптимизации лечения нарушений когнитивных функций, индуцируемых длительной гипергликемией, можно считать совместное назначение препаратов с имеющейся антигипергликемической и ноотропной активностью, в частности, метформина с пирацетамом. Показано, что в условиях экспериментальной аллоксан-индуцированной гипергликемии пирацетам обладает недостаточным ноотропным потенциалом для устранения когнитивного дефицита. Метформин оказывает незначительное ноотропное действие при краткосрочном*

использовании в низких дозах, при этом не проявляя этих свойств при длительном введении. Показано, что при сочетанном применении с пирацетамом метформин потенцирует его антиамнестические свойства, что способствует восстановлению когнитивных функций, ослабленных гипергликемией. Предполагается, что механизмы такого синергизма опосредуются снижением содержания ранних и поздних маркеров деструкции белковых молекул, уровня стабильных метаболитов оксида азота в коре головного мозга, а также существенным ограничением проявлений ультраструктурных деструктивных изменений нейронов гиппокампа с одновременным улучшением состояния его микроциркуляторного русла. Полученные результаты указывают на целесообразность использования метформина совместно с ноотропами для предупреждения или лечения когнитивных нарушений, которые возникают вследствие сахарного диабета.

Diabetes mellitus (DM) which is considered a non-infectious epidemic of the XXI century is now recognized as an independent risk factor for diabetic encephalopathy, which is characterized by the progressive development of cognitive dysfunction. The most significant mechanisms of DM manifestations include impairment of the integrity of the blood-brain barrier, hyperglycemia, insulin resistance, vascular dysfunction of the microcirculatory tract and endothelium [2].

The development of cognitive disorders in patients with diabetes mellitus is primarily mediated by chronic hyperglycemia, which causes the activation of mechanisms of CNS damage, manifested primarily by induction of apoptosis of neurons of the hippocampus-amygdala complex [7]. Endothelial dysfunction is considered a universal mechanism for the development of memory deficits in diabetic encephalopathy [3], as diabetes alters endothelial function and the permeability of the blood-brain barrier, thereby impairing blood flow and regional metabolism in the brain [5]. The processes of cognitive aging in DM patients are also to some extent explained by the concept of "insulin resistance of the brain." Depletion of insulin receptors in the central nervous system is accompanied by weakening of the neuroprotective effect of insulin with the subsequent development of hippocampus dysfunction, cognitive disorders and mnestic deficiency [4].

Given that strategically important links in the pathogenesis of memory disorders in DM patients are chronic hyperglycemia, insulin resistance and endothelial dysfunction [2], one of the current trends in optimizing the treatment of cognitive impairment should be considered concomitant use of drugs with existing antihypertensive and nootropic activity; this determined the purpose of this experimental study.

The aim of our work was to experimentally determine the feasibility of using a combination of metformin with piracetam as a means of pharmacological correction of cognitive impairment in conditions of prolonged hyperglycemia.

MATERIALS AND METHODS OF RESEARCH

The study used 70 white mature Wistar rats weighing 230-350 g. The animals were kept in standard vivarium conditions with free access to water and food in inverted light conditions 8.00-20.00 at an air temperature of 22±2°C.

The experiment was conducted on the basis of the Department of Pharmacology and Clinical Pharmacology of the State Establishment "Dnipropetrovsk Medical Academy of Health Ministry of Ukraine" (Dnipro). All procedures (anesthesia, administration of drugs, withdrawal of animals from the experiment, etc.) fully complied with the principles of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Strasbourg, 1986), Directives 2010/63/EU on the protection of animals used for scientific purposes (2010), the Law of Ukraine "On the protection of animals from cruel treatment" and the conclusion of the Commission on Biomedical Ethics of the SE “DMA” (Protocol N 8 of 17.12.2019).

Animals were divided into five main groups (n=50), the group of active (alloxan diabetes, n=10) and the group of passive intact (n=10) control. Aqueous solution of alloxan monohydrate at a dose of 150 mg/kg as a 5% solution in citrate buffer, pH 4.5 was administered subcutaneously to all animals of the main groups and active control group to reproduce the experimental state of prolonged hyperglycemia. Blood glucose levels were determined on day 11 after alloxan administration using an Optium Omega glucometer (Abbot Diabetes Care Inc., USA). For further studies, only animals with elevated glucose levels (>11 mmol/L) were used. A group of intact animals received subcutaneous saline in appropriate volumes.

In order to study the state of cognitive functions of the brain to the extent that alloxan-induced pathology of the pancreas progresses and the effect of experimental drugs with existing antihyperglycemic and nootropic activity on the course of this process, rats of the 1st, 2nd and 3rd main groups (n=10 each) were administered metformin intragastrically once a day for 20 days at doses equivalent to the daily therapeutic range for humans: 250, 500 and 750 mg/kg, respectively (Glucophage®, 500 mg tablets, Merck Santé SAS, France). Rats of the 4th main group (n=10) were administered piracetam

intragastrically once a day for 20 days at a dose of 400 mg/kg (Lucetam® (piracetam), tablets 1200 mg, the company "Egis Pharmaceuticals PLC", Hungary), of the 5th group (n=10) – a combination of these drugs (metformin 250 mg/kg + piracetam 400 mg/kg) in a similar mode. The animals of the active control group were injected distilled water intragastrically Evaluation of the effectiveness of experimental therapy was performed on day 6 and 20 after the introduction of experimental drugs in the test of the conditioned reaction of passive avoidance (CRPA). The latent period (LP) of the animals entering the dark compartment of the chamber and the level of amnesia of the conditional skill served as an assessment indicator of the CRPA skill reproduction [9].

As alloxan hyperglycemia (AH) progressed, blood glucose levels, activity of free radical oxidation processes, and nitric oxide metabolism in rat neocortex homogenates, vascular endothelial function, and ultrastructural changes in the brain-blood barrier (BBB) and vascular stream of the hippocampus were assessed.

Blood glucose levels were assessed on day 20 of the experiment in rats of all groups using an Optium Omega glucometer (Abbot Diabetes Care Inc., USA).

Markers of oxidative stress were the levels of products of oxidative modification of protein molecules – aldehydephenylhydrazones (APHs) and ketonephenylhydrazones (CPHs), and of the state of the nitric oxide metabolism – the level of its stable metabolites NO_x in the neocortex. To determine them on day 20, rats of the 4th and 5th main groups, as well as active and intact control groups were withdrawn from the experiment by decapitation under light ether anesthesia, followed by blood sampling and extraction of neocortex tissues, of which hemogenates were prepared. The content of APH and CPH [15], as well as NO_x [6] in homogenates of the cerebral cortex was determined spectrophotometrically by conventional methods.

The study of endothelial platelet homeostasis was performed on day 20 in rats of the 5th main group, as well as active and intact control groups by assessing the systemic production of endothelial nitric oxide and the activity of constitutive NOS in platelets. The level of stable NO_x metabolites [6] was determined spectrophotometrically, and the content of the physiological isoforms of nitric oxide synthase in the platelet suspension according to the level of difformazan was determined [8].

Evaluation of ultrastructural changes of the BBB and the vascular stream of the hippocampus was performed using a transmission electron microscope PEM-100-01 ("SELMI", Ukraine) at an acceleration voltage of 70-75 kV and primary voltage increases from 4000 to 20,000 according to the standard scheme with preliminary preparation of the material according to generally accepted standards [11].

The data obtained in the experiment were processed by biostatistics methods using the program STATISTICA 6.1 (serial number AGAR 909 E415822FA). The reliability of intergroup differences was established using Student's parametric t-test, Wilcoxon rank sum test, Mann-Whitney test, and ANOVA one-way analysis of variance [1].

The level of reliability of statistical significance of differences in research results was $p<0.05$; $p<0.01$ and $p<0.001$.

RESULTS AND DISCUSSION

According to our results, the course of a 20-days intragastric administration of metformin at a dose of 250 mg/kg led to a decrease in glucose levels by 14.8% ($p<0.05$) only compared with day 1 of the experiment, but not of the active control group. In turn, in using metformin at a dose of 500 mg/kg glucose levels at the end of the experiment were lower by 18.9% ($p<0.05$) relative to baseline and by 21.9% ($p<0.01$) – relative to animals of AH group. With repeated injections of the drug at a dose of 750 mg/kg, these indicators were lower by 28.7% ($p<0.05$) and 25.7% ($p<0.01$), respectively (Table 1).

Thus, metformin in conditions of chronic hyperglycemia dose-dependently reduces its degree, but in the studied doses does not lead to complete recovery of physiological blood glucose levels. The obtained results are in agreement with the literature data, this shows that the main function of metformin is the regulation of glucose homeostasis, primarily by influencing the processes of gluconeogenesis and glycogenolysis in hepatocytes [14], which is mediated by a number of mechanisms: inhibition of mitochondria hepatocytes and antagonism with the glucagon signaling pathway [12].

The analysis of the study of mnestic functions state showed that in animals with AH there were pronounced manifestations of cognitive deficits. In particular, on day 6 of CRPA testing, the duration of LP was reduced by 56% ($p=0.064$) compared with passive control, and on day 20 – by 61.5% ($p<0.05$) in relation to the value of the corresponding indicator in group of intact animals (Table 2).

It was proved that the course of intragastric administration of metformin at different doses to rats with hypertension on day 6 of CRPA testing was characterized by a pronounced tendency to increase the duration of LP only when using a test hypoglycemic agent at a dose of 250 mg/kg, which caused an increase of indicator by 2.78 times ($p=0.05$)

compared with the active control group. The level of amnesia of animals on day 20 after the introduction of metformin in all dose regimens was close to the indicators of the active control group (Table 2).

Table 1

Level of blood glucose in rats with alloxan-induced hyperglycemia under conditions of experimental therapy with metformin (M±m, n=10)

Group of animals	Glucose level, mmol/L	
	day 1	day 20
Passive control (intact)	5.91±0.410	5.51±0.315
Active control (AH)	18.08±1.269***	17.47±1.143***
Metformin (250 mg/kg)	16.52±0.805***	14.08±0.797$^{\times}$
Metformin (500 mg/kg)	16.84±1.067***	13.65±0.882$^{\#\times\times}$
Metformin (750 mg/kg)	18.19±1.463***	12.97±1.135$^{\#\times\times}$

Notes: *** – p<0.001 in relation to passive control indices; **# –** p<0.05 – in relation to indices of AH group; $^{\times}$ – p<0.05; $^{\times\times}$ **–** p<0.01 **–** in relation to indices of day 1 of the study.

It was noted that intragastric administration of piracetam at a dose of 400 mg/kg in animals with prolonged hyperglycemia contributed to some increase in the duration of the latent period compared with the active control group, which, however, was not statistically significant. In turn, the combined use of piracetam with metformin (400/250 mg/kg) was characterized by prolongation of LP on day 6 and 20 of the experiment by 3.44 (p<0.01) and 4.94 (p<0.001) times, respectively, relative to a similar indicator of the AH group. At the same time, the values of the LP of the acquired skill registered in animals of this group were statistically significantly higher than the indicators of the piracetam group (Table 2).

Table 2

Duration of latent period of CRPA in rats with alloxan-induced hyperglycemia under conditions of repeated administration of metformin and its combination with piracetam (M±m, n=10)

Conditions of experiment	Latent period, sec.		
	day 5	day 6	day 20
Passive control (intact)	22.7±4.65	173.5±6.50	165.3±14.70
Active control (AH)	20.8±1.99	42.7±10.75 (p=0.06)	33.3±9.39*
Metformin (250 mg/kg)	18.6±3.81	118.8±25.13 (p = 0.05)	48.9±9.63
Metformin (500 mg/kg)	22.2±4.79	94.1±21.62	40.1±8.28
Metformin (750 mg/kg)	20.6±3.43	92.6±24.76	47.8±17.13
Piracetam (400 mg/kg)	19.3±3.99	104.0±25.67	85.3±26.09
Piracetam (400 mg/kg) + metformin (250 mg/kg)	18.1±3.15	146.8±22.13$^{\#\#}$	164.5±15.50$^{\#\#\#}$

Notes: * **–** p<0.05 – in relation to group of passive intact control; $^{\#\#}$ **–** p<0.01; $^{\#\#\#}$ – p<0.001 – in relation to group of active control (AH).

Thus, prolonged hypertension initiates processes that lead to amnesia of the acquired skill and, thus, causes the development of cognitive deficits. Metformin contributes to a dose-dependent decrease in glucose levels and, under conditions of short-term administration, in a low-dose regimen (250 mg/kg) shows some nootropic and antiamnestic activity but does not show these properties at 3 weeks of use. And experimental piracetam therapy is not able to fully prevent the development of cognitive deficits in hypertension and inhibit its further growth. Metformin, when used in combination with piracetam, potentiates the anti-amnestic properties of the nootropics and helps to restore cognitive functions suppressed by prolonged hyperglycemia.

It is quite probable that such a feature of combination therapy is mediated by the synergism of the mechanisms of influence of the ingredients of this composition on strategically important links in the pathogenesis of cognitive deficits caused by prolonged hyperglycemia. Thus, according to our results, the course of prolonged alloxan-induced hyperglycemia in rats significantly accelerated the intensity of oxidative modification of protein in the cerebral cortex, as evidenced by an increase in the concentration of APH and CPH by 82.2% ($p<0.001$) and 44.3% ($p<0.001$), respectively (Table 3).

It was shown that repeated, within 20 days, intragastric administration of piracetam at a dose of 400 mg/kg contributed to a decrease in the content of markers of OMP in the neocortex to a greater extent in relation to CPH, the level of which was 12.6% ($p<0.01$) lower compared to the active control group. The course of combination therapy with piracetam (400 mg/kg) and metformin (250 mg/kg) contributed to a decrease in the content of APH and CPH compared with the active control group by 35% ($p<0.01$) and 21.1% ($p<0.05$) respectively, and at the same time was more effective than monotherapy with piracetam as in relation to APH – a decrease by 30.5% ($p<0.05$) and CPH – by 9.6% ($p<0.05$).

Table 3

Effect of piracetam and its combination with metformin on the content of products of oxidative modification of proteins, stable metabolites of nitric oxide in neocortex homogenates, blood glucose in rats with alloxan-induced hyperglycemia (M±m, n=10)

Group of animals	APH c.u./g. of protein	CPH c.u./g. of protein	NO_x, mcmol/L	Glucose, mmol/Lл
Passive control (intact)	0,75±0,056	1,15±0,036	22,3±3,29	6,7±0,55
Active control (AIH)	1,37±0,074*	1,66±0,044*	45,7±6,25*	20,8±2,19*
Metformin (250 mg/kg)	1,28±0,078	1,45±0,040$^{\#\#}$	37,6±2,90	18,8±1,97
Metformin (500 mg/kg)	0,89±0,092$^{\#\#\times}$	1,31±0,082$^{\#\times}$	29,7±3,32$^{\#}$	13,6±1,16$^{\#}$
Metformin (750 mg/kg)				

Notes: * – $p<0.001$ – in relation to indices of passive control; $^{\#}$ – $p<0.05$; $^{\#\#}$ – $p<0.01$ – in relation to group of active control; $^{\times}$ – $p<0.05$ – in relation to indices of piracetam group.

It was found that the reproduction of the experimental equivalent of diabetes in rats was accompanied by an increase in systemic nitric oxide production in the cerebral cortex: the level of stable NO_x metabolites in the neocortex increased by 2.05 times ($p<0.001$) compared with the intact control group (Table 3).

It was proved that a statistically significant decrease in the content of stable metabolites of nitric oxide was observed only in the group of a course combined use of piracetam with metformin, after the introduction of which the NO_x level decreased by 32.8% ($p<0.05$) relative to the same indicator in the group of AH. At the same time, a statistically significant decrease in blood glucose levels by 34.6% ($p<0.05$) compared with the active control group was also observed only with 20-day co-administration of piracetam with metformin, but not with piracetam monotherapy (Table 3).

Thus, the course of prolonged alloxan-induced hyperglycemia in rats is accompanied by an intensification of the processes of free radical oxidation of protein molecules, as well as an increase in the systemic production of nitric oxide in the

neocortex. Piracetam used in combination with metformin statistically significantly reduces the content of early and late markers of destruction of protein molecules, as well as the level of stable metabolites of nitric oxide.

The results correlate with literature data that hyperglycemia enhances the production of active forms of oxygen (AFO) in mitochondria, thereby inducing oxidative stress, which leads to oxidative modification of lipids, proteins and DNA, and ultimately - to apoptosis of cells [12]. In addition, the hyperglycemia-induced increase in nitric oxide pool facilitates the reaction of its interaction with the superoxide anion radical, which results in the formation of perosynitrite, which exhibits a much greater destructive ability than nitric oxide or superoxide anion [10]. Metformin, acting as a promoter of the antioxidant defense system, enhances the direct "capture" of the hydroxyl radical (OH •) – the main agent that causes destructive processes in the cell; increases the activity of endogenous antioxidant enzymes (glutathione reductase, catalase and superoxide dismutase); inactivates NADPH oxidase, leading to an increase in the cytosolic content of NADPH and, consequently, levels of reduced glutathione that weakens the oxidative stress, which plays a role in the pathogenesis of many diseases, including diabetes. In addition, increasing level of intracellular glutathione is likely to prevent the binding of the NO molecule to the superoxide anion, thereby preventing the formation of peroxynitrite and have a specific cytoprotective effect [12].

Analysis of the effect of the combination of piracetam with metformin on the functional state of the vascular endothelium of rats with AH showed that prolonged hyperglycemia was accompanied by a decrease in the level of stable metabolites of NO_x by 36.2% ($p<0.05$) compared with the passive control group. Piracetam in combination with metformin (400/250 mg/kg) contributed to a statistically significant increase in the pool of physiological isoform of nitric oxide synthase in platelets of rats by 17.5% ($p<0.05$) compared with the AH group, but did not lead to complete restoration of its activity to the level of a group of intact animals (Table 4).

Table 4

Level of stable metabolites of nitric oxide in blood plasma and constitutive NO synthase activity in platelets of rats with AIH under the conditions of administration of piracetam and its combination (M±m, n=10)

Groups of animals	NO_x, mcmol/L	Activity of NOS, nmol/min/10^8 thrombocytes
Passive control (intact)	**42,72±5,358**	**16,89±0,809**
Active control (AIH)	**27,26±3,144***	**10,72±0,356***
Metformin (250 mg/kg)	**33,03±3,892**	**12,44±0,629#**
Metformin (500 mg/kg)	**29,92±4,809**	**12,60±0,654#**
Metformin (750 mg/kg)		

Notes: * - $p<0.05$ – in relation to indices of passive control; # – $p<0,05$ – in relation to indices fixed in group of active control.

Thus, the combination of metformin and piracetam in alloxan-induced hyperglycemia increases the content of constitutive NO-synthase of nitric oxide in platelets, which to some extent may indicate a positive effect of combination on the rheological properties of blood. Prolonged hyperglycemia as a result of sustained activation of NADPH oxidase is known to reduce the intracellular pool of NADPH, which is required as a cofactor of endothelial NO synthase and thus reduces NO generation and endothelium-dependent vasodilation [12]. Metformin is able to modulate the effect of hyperglycemia on endothelial function by increasing the phosphorylation of eNOS [13].

According to the results of transmission electron microscopy, in the wall of the arterioles of the frontal hippocampus of animals with alloxan-induced hyperglycemia there was a sharp thickening and loosening of the basement membrane, mosaic dystrophy, edema of endothelial cells and proliferation of pericytes (Fig. 1) as compared to ultrastructure of the arterioles of the hippocampus of

intact animals (Fig. 2). The combined administration of piracetam and metformin (400/250 mg/kg) significantly limited the intramural edema of arterioles and venules (Fig. 3).

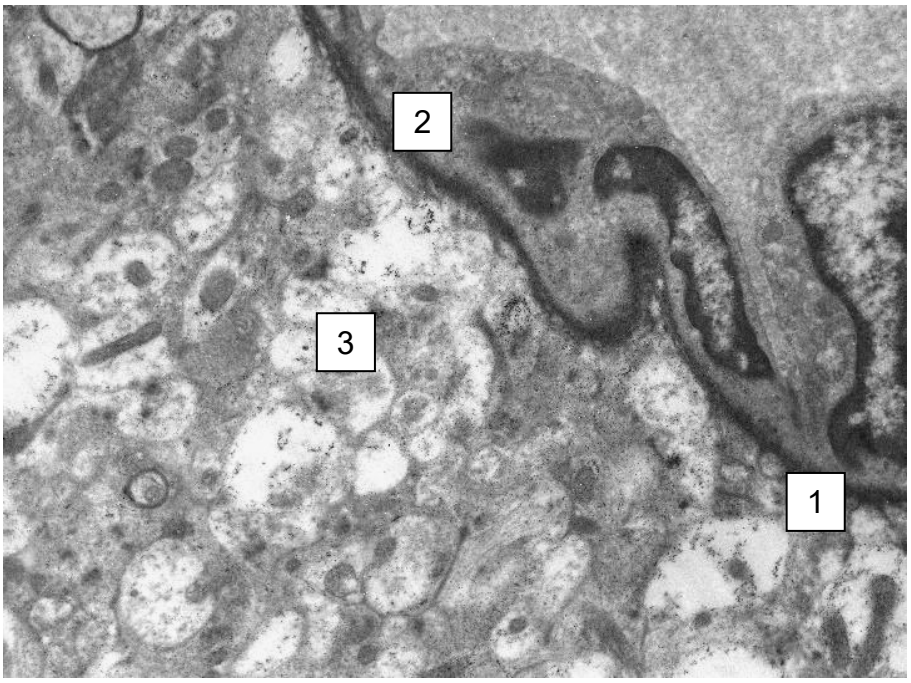

Fig. 1. Hippocampus of rats with alloxan diabetes. Area of arteriole wall. Thickening of the basement membrane (1), dystrophy and swelling of endothelial cells (2). Severe perivascular edema (3). × 10000

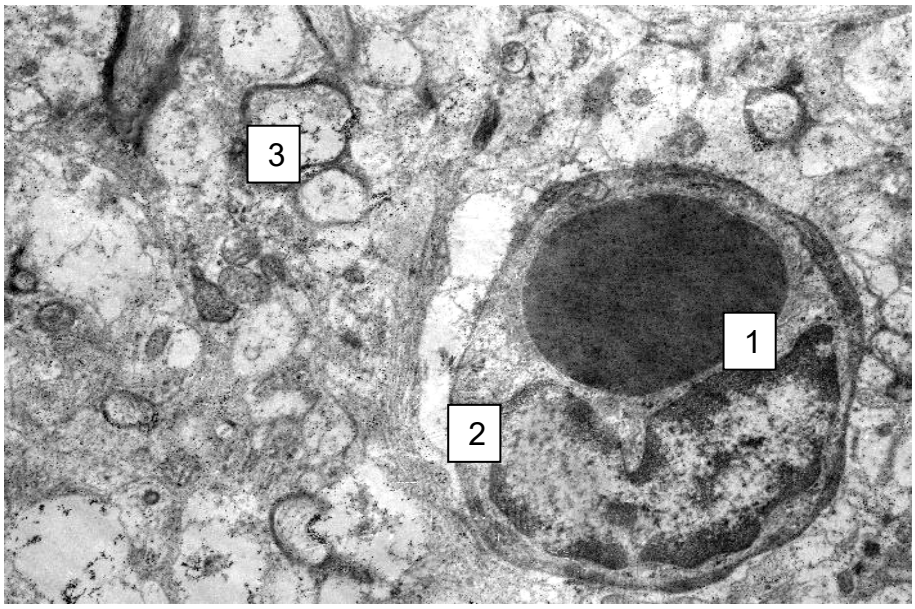

Fig. 2. Hippocampus of the rat group of passive control. Hemocapillary (1), blood-brain barrier structures (2) and cross sections of nerve fibers (3). Electronogram ×10000

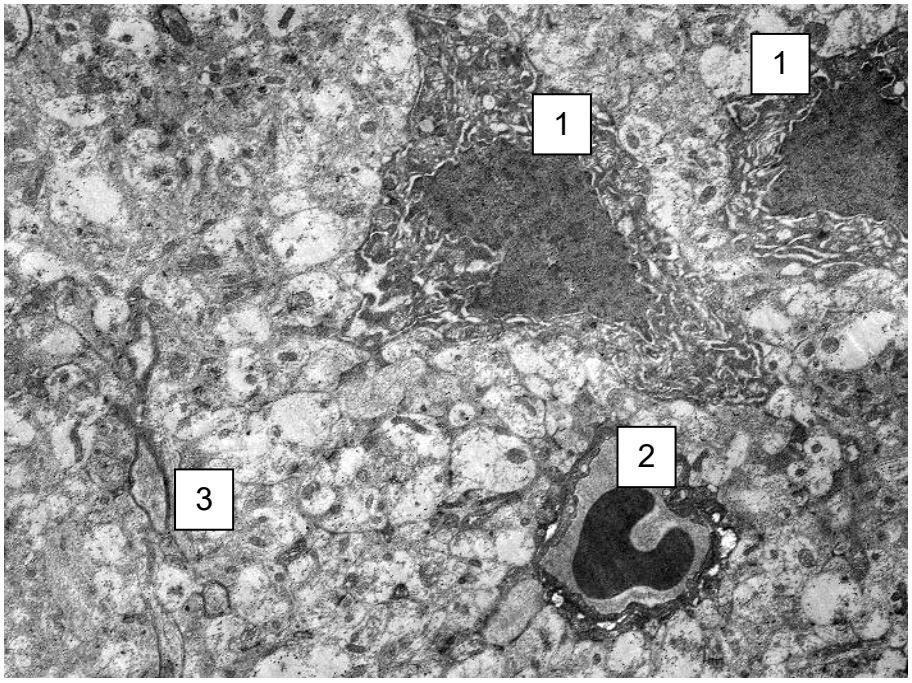

**Fig. 3. Hippocampus of rats with alloxan diabetes. Piracetam + metformin (400/500 mg/kg)
Pyramidal neurons with minor disorders of ultrastructure (1).
Precapillary arteriole (2). Slight diffuse edema of tissue (3). Electronogram × 5000**

It is shown that the dysfunction of the vascular apparatus was represented by moderate thickening and loosening of the basement membrane, dystrophy and edema of endothelial cells. A slight perivascular edema around the microvessels of the afferent and metabolic links of the hemato-microcirculatory tract was observed as well. The wall of hemocapillaries had an integral structure, without areas of fragmentation of the endothelium or basement membrane. The interendothelial connections and the length of the interendothelial fissures were close to normal values (Fig. 3).

Thus, the analysis of the studies shows that alloxan-induced hyperglycemia in rats leads to significant ultrastructural changes in both the neuronal apparatus and the blood-brain barrier in the hippocampus of experimental animals, which are a prerequisite for the destruction of neurons and subsequent initialization of apoptosis processes. The course of experimental therapy, based on the simultaneous combined use of piracetam with metformin is not able to fully ensure the restoration of ultrastructural changes in the hippocampus, but significantly limits the manifestations of destructive changes in neurons, while improving the microcirculatory system. The data obtained generally agree with the degree of antiamnestic activity of this drug combination, which indicates the feasibility of using metformin in combination with nootropics to prevent or treat cognitive impairment caused by diabetes.

CONCLUSIONS

1. Alloxan-induced hyperglycemia, acting as an amnesic factor, causes the development of cognitive deficits.
2. Metformin in conditions of prolonged hyperglycemia shows insignificant nootropic activity with short-term use in low doses, without showing these properties in prolonged administration.
3. When used in combination with piracetam, metformin potentiates the anti-amnestic properties of piracetam and helps to restore lost cognitive functions.
4. Metformin in combination with piracetam reduces the content of early and late markers of destruction of protein molecules, as well as the level of stable metabolites of nitric oxide in the cerebral cortex.
5. Combined course administration of piracetam with metformin significantly limits the manifestations of destructive changes in the hippocampus neurons, improving the state of its microcirculatory tract.

Prospects for further research. The presented research results are the initial link in determining the features of neuroprotection in conditions of chronic hyperglycemia and insulin resistance and require further study of the mechanisms of endothelial protection in the use of hypoglycemic drugs.

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