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Research Article

Correction by neuroglutam and succicard of age-associated impairments in accelerated aging in rats with diabetes

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Abstract

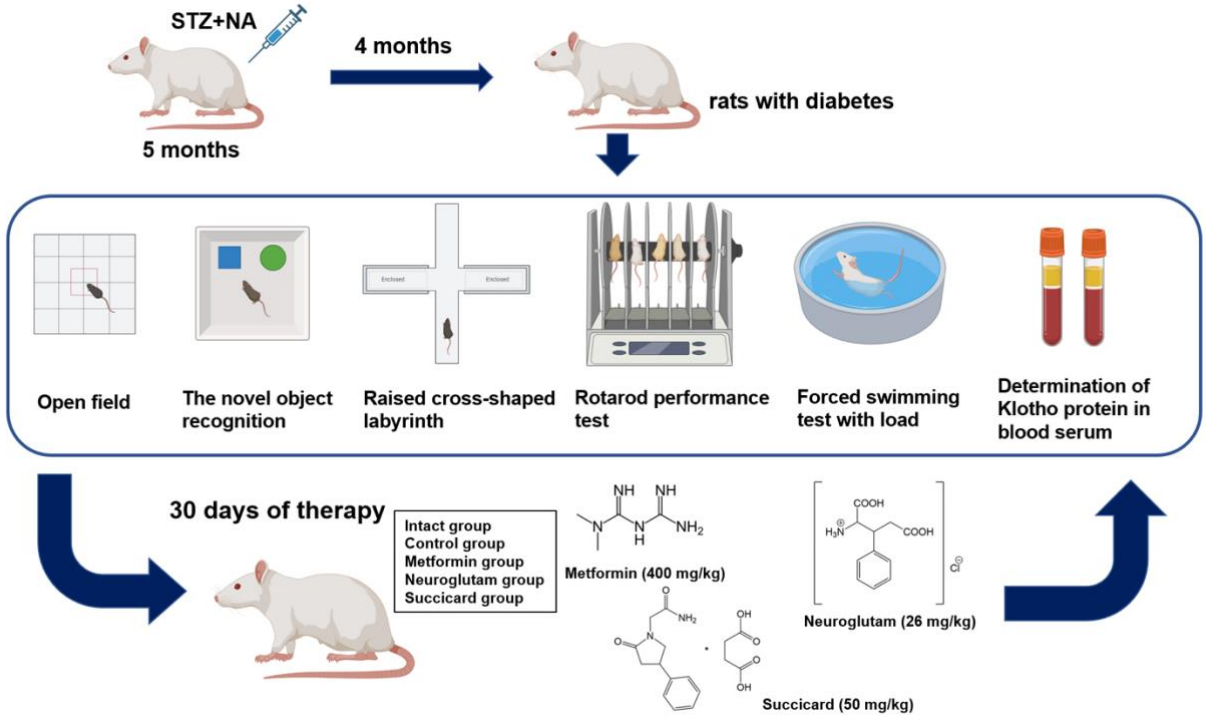
Introduction: The study aimed to investigate the impact of a long-term diabetic state on the development of accelerated aging and to evaluate the efficacy of therapy with metformin, neuroglutam, and succicard in correcting associated metabolic, behavioral, and molecular impairments.

Materials and Methods: A diabetes model was induced in rats by combined administration of streptozotocin (50 mg/kg) and nicotinamide (110 mg/kg). The total number of animals involved in the experiment was 50 individuals (25 males, 25 females). The animals were divided into 5 groups: intact, control (diabetic), and groups receiving a 4-week course of metformin (400 mg/kg), neuroglutam (26 mg/kg), or succicard (50 mg/kg). A comprehensive assessment was performed, including behavioral tests (open field, elevated cross maze, novel object recognition, forced swimming with a load, rotarod), metabolic status (oral glucose tolerance test, OGTT), and Klotho protein levels (ELISA).

Results: Diabetes induced anxiety-like behavior, cognitive decline, impaired motor coordination, and a significant decrease in Klotho protein levels. Therapy with metformin and succicard significantly increased Klotho protein levels and improved metabolic parameters. Neuroglutam exhibited pronounced nootropic and antidepressant-like effects. All drugs demonstrated differential effects on various aspects of behavioral activity.

Conclusion: The study demonstrates the potential of using metformin (400 mg/kg), neuroglutam (26 mg/kg), and succicard (50 mg/kg) to correct the manifestations of accelerated aging in diabetic rats with daily administration for 4 weeks. Metformin and succicard showed the most pronounced geroprotective potential. The results justify further investigation of combination therapy for correcting age-associated impairments.

Graphical Abstract



Keywords

accelerated aging, GABA derivatives, Klotho protein, diabetes

Introduction

According to the World Health Organization, the aging of the population represents one of the key medico-social problems, driving an intensive search for approaches to treat age-associated pathologies and extend the healthspan. Studying the process of accelerated aging, which develops against the background of various chronic diseases such as type 2 diabetes mellitus (T2DM) and diabetes, is of particular relevance (Dove et al. 2024). Numerous studies indicate that hyperglycemia and insulin resistance, the main features of these conditions, trigger a cascade of pathological processes (oxidative stress, chronic inflammation, accumulation of advanced glycation end-products) that directly damage cells and accelerate their aging (Darenskaya et al. 2021; Weinberg et al. 2024). This manifests not only in the development of specific diabetic complications (neuropathy, retinopathy, nephropathy) but also in a systemic decline in body functions, including cognitive and motor impairments similar to those in physiological aging (Sagoo and Gnudi 2020; Galiero et al. 2023; Dao et al. 2023). Diabetes, as an intermediate state between normal and T2DM, often remains undiagnosed; however, even at this stage, initial metabolic disturbances and potentially irreversible changes in target organs, including the central nervous system (CNS), are observed (Echouffo-Tcheugui et al. 2023).

An important biomarker linking metabolism and aging is the Klotho protein. This transmembrane protein, expressed primarily in the kidneys and brain, plays a key role in regulating insulin sensitivity, phosphate metabolism, and possesses cytoprotective properties (Shen et al. 2025). Decreased levels of Klotho, both in serum and tissues, are associated with accelerated aging, the development of age-related diseases including T2DM and its complications, as well as cognitive decline (Prud'homme et al. 2022). Restoring Klotho levels is considered a promising therapeutic strategy.

Gamma-aminobutyric acid (GABA) is a key inhibitory neurotransmitter in the CNS; however, its receptors are also expressed in peripheral organs, including the pancreas. Experimental data show that GABA suppresses apoptosis of pancreatic β-cells, stimulates their

proliferation, and increases functional β-cell mass (Tyurenkov et al. 2023a, Tyurenkov et al. 2023b). It is also known that GABA derivatives have a neuroprotective effect and can reduce cognitive deficits (Tyurenkov et al. 2023). In addition to pronounced effects on the pancreas and CNS, GABA influences the expression of the Klotho protein, increasing its concentration in blood serum (Prud'homme et al. 2017). Thus, GABA derivatives represent a class of compounds promising for the search of substances to correct both metabolic disorders in diabetes and concomitant accelerated aging. In this regard, we decided to evaluate the effects of a 4-week therapy with metformin, neuroglutam, and succicard on behavioral (cognitive and emotional-affective) and motor functions, blood glucose levels, and Klotho protein expression in rats with STZ-induced diabetes modeling a state of accelerated aging.

Materials and Methods

Study objects

All experiments were performed in accordance with the legislation of the Russian Federation and the technical standards of the Eurasian Economic Union for Good Laboratory Practice (GOST R 53434-2009, GOST R 51000.4-2011). The study design and protocol were approved by the Local Ethical Committee of Volgograd State Medical University, Minutes No. 2025/024 dated March 28, 2025 (registration number IRB 00005839 IORG 0004900 [OHRP]).

Investigated compounds

Neuroglutam (beta-phenylglutamic acid hydrochloride) is a compound containing 5 pharmacophoric groups in its structure: GABA, phenibut, glutamic acid, glycine, and phenylethylamine, which is associated with a broad spectrum of pharmacological action. It has antihypoxic, neuroprotective, and antioxidant effects, capable of improving the body's resistance to damaging influences (Bagmetova et al. 2018).

Succicard (4-phenylpiracetam combined with succinic acid, 2:1) has a proven neuroprotective effect and is also capable of increasing Klotho levels in blood plasma, brain, and renal tubular epithelium (Smirnov et al. 2024; Kavalerova et al. 2023).

Metformin is a first-line drug for the treatment of type 2 diabetes mellitus; its main effects include suppression of hepatic gluconeogenesis, enhanced glucose utilization in peripheral tissues, and improved insulin sensitivity. In addition to proven hypoglycemic properties, metformin has potential geroprotective properties mediated through inhibition of the mTOR signaling pathway, reduction of oxidative stress, and activation of autophagy. An important feature of metformin is its ability to modulate cellular senescence processes and potentially influence Klotho protein expression, making it a promising drug for correcting age-associated impairments (Piskovatska et al. 2019).

Modeling the pathology

A diabetic state was induced in 5-month-old rats by combined administration of streptozotocin and nicotinamide via a single intraperitoneal injection of streptozotocin (60 mg/kg) 15 minutes after preliminary administration of nicotinamide (230 mg/kg). Prior to this, 12 hours beforehand (overnight), the animals were food-deprived with free access to water. Streptozotocin (Sigma-Aldrich, USA) was dissolved immediately before administration in cold citrate buffer (1 mM, pH 4.5) in a dark container; nicotinamide was dissolved in 0.9% NaCl physiological saline. At the age of 9 months, an oral glucose tolerance test (OGTT) was performed on all animals. Animals meeting one or two diagnostic criteria were included in the experiment: peak blood glucose concentration during the test exceeded 16 mmol/L and/or the glucose level at the 120th minute was greater than 11 mmol/L (Wang et al. 2021). Blood glucose levels were measured using a Contour TS glucometer and corresponding test strips (Bayer, Japan). Blood for measurements was obtained by puncture of the sublingual vein. The formed experimental groups were sex-balanced: each group consisted of 10 animals (5 males and 5 females), allowing for consideration of potential sex differences in the course of metabolic disorders and sensitivity to the action of the investigated substances.

Study design

After establishing the diabetes model and selecting animals according to the impaired glucose tolerance criteria, the rats were randomly allocated into six experimental groups (n=10 each, 5 males and 5 females): 1) Intact group (healthy animals receiving purified water); 2) diabetes control group (diabetic animals receiving purified water); 3-5) diabetes groups receiving a 4-week therapy with metformin (400 mg/kg), neuroglutam (26 mg/kg), or succicard (50 mg/kg), respectively. All animals underwent a comprehensive assessment before the start of treatment

and after its completion: OGTT, psycho-neurological status testing (open field, elevated cross maze, novel object recognition test (NOR)), assessment of physical performance and coordination (forced swimming with a load, rotarod), and determination of serum Klotho protein concentration by enzyme-linked immunosorbent assay (ELISA). All investigated substances were dissolved in purified water and administered daily for 30 days intragastrically via a metal gavage tube, followed by an additional 2 weeks during sequential testing.

Methods of behavioral testing

A standardized battery of behavioral tests was used for a comprehensive assessment of the animals' functional state. The open field test was conducted in a round arena 100 cm in diameter; over 3 minutes, horizontal (distance traveled) and vertical (rearing on hind legs) activity, as well as the number of hole pokes, were recorded to assess exploratory activity. Total exploratory activity was calculated by summing the number of unsupported rears, rears supported against the wall, and hole pokes.

The elevated cross maze was used to assess anxiety-like behavior: the time spent and the number of entries into the open and closed arms over 3 minutes were recorded, as well as the latency to leave the central platform after placing the rat on the apparatus.

The novel object recognition test was conducted to assess the ability to detect and compare information stored in short-term memory. The test consisted of two phases (familiarization phase and testing phase with one object replaced by a novel one) with a 1-hour interval. The discrimination index (DI) was calculated from the test results – time spent exploring the novel object (B) minus time spent exploring the old object (A) in the second trial.

Assessment of physical performance and motor coordination

The forced swimming with a load test was conducted to assess physical endurance. The animal was placed in a vertical cylinder filled with water (temperature 25 ± 1 °C). A load weighing 7% of the animal's body weight was attached to the rat's tail. A total of 3 swimming sessions were conducted, with a 60-minute interval between sessions. The animal's submersion underwater and inability to surface for 10 seconds were considered the end of testing in that particular swim session. The average swimming time over 3 attempts was calculated after the tests.

The Rotarod test was used to assess motor coordination and dynamic balance. The animals were pre-trained on a rotating rod (7 cm in diameter, rotation speed of 10 rpm) for 60 seconds. On the following day, testing was conducted at a speed of 10 rpm, recording the latency to fall from the rod over 3 trials.

Enzyme-linked immunosorbent assay

ELISA was performed using commercial kits (Cloud-Clone Corp., USA) according to the manufacturer's instructions. The analysis utilized the blood serum. Optical density was measured using a SPECTROstar Nano microplate automatic analyzer (BMGLabtech, Germany).

Statistical analysis

Statistical analysis was performed with Microsoft Office Excel 2016 (Microsoft, USA) and Prism 10 (GraphPad Software Inc., USA). The normality of the data distribution in each group was evaluated by the Shapiro–Wilk test. Homogeneity of variances was tested by means of the Brown–Forsythe test. The intergroup differences were assessed using the Kruskal-Wallis rank analysis and the Dunn post-hoc test. All data presented as the mean and standard error of the mean (SEM). The differences were considered statistically significant at $p<0.05$.

Results and Discussion

Analysis of OGTT data conducted before the start of therapy confirmed the presence of pronounced carbohydrate metabolism disorders in all animals with modeled diabetes (Fig. 1). Blood glucose levels in the diabetes groups statistically significantly exceeded the indicators of the intact group by 64%, objectively indicating a reduced rate of glucose utilization and, accordingly, impaired glucose tolerance. After the course of therapy, pronounced positive dynamics were revealed in the treatment groups. In the metformin, neuroglutam, and succicard groups, to varying degrees of severity, a statistically significant increase in the rate of glucose utilization compared to the control group was noted at all measurement time points: 30, 60, and 120 minutes. The obtained results indicate markedly better glucose utilization with the reference drug metformin, to a lesser extent with neuroglutam, and even less with succicard. The subsequent goal was to assess the physical and psycho-emotional state of the animals.

The results of the open field test are presented in Figure 2. The conducted open field test

revealed significant differences in exploratory, motor, and spontaneous activity indicators between intact animals and control diabetic animals. Comparing the spontaneous motor and exploratory activity indicators of the control group animals with those receiving succicard and metformin, the indicators were significantly higher (by 54% and 45%, respectively) than in the control diabetic group, expressed in a greater number of rears and hole pokes. Furthermore, a significant increase in the distance traveled was recorded in the groups receiving neuroglutam and succicard compared to the control group.

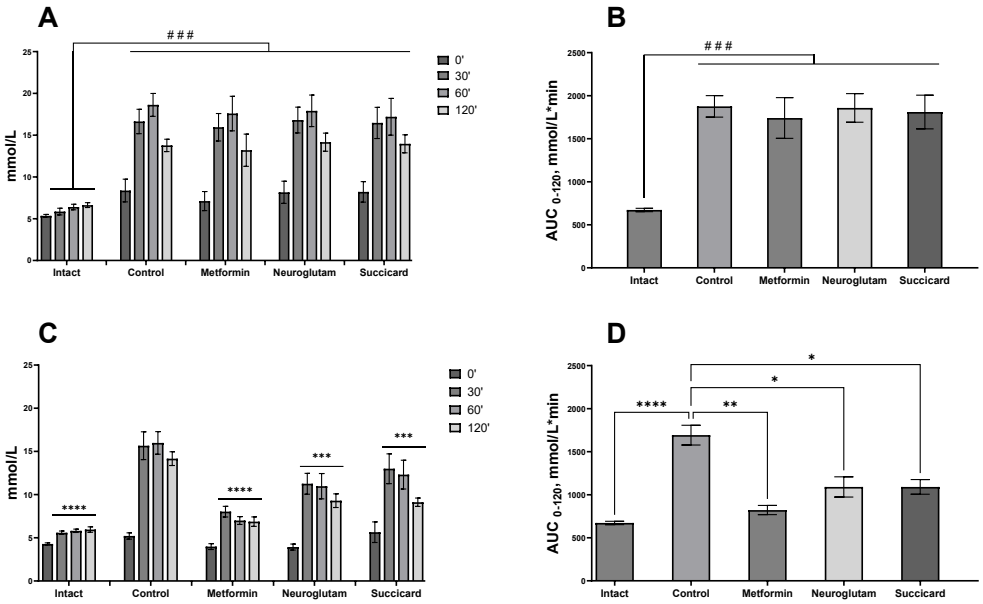


Figure 1. Results of the OGTT test before treatment (**A**); area under the curve "glucose level-time" before treatment (**B**); results of the OGTT test after treatment (**C**); area under the curve "glucose level-time" after treatment (**D**). ***Note:*** ### – p<0.001 compared to Intact group, * – p<0.05 compared to control group; ** – p<0.01 compared to control group; *** – p<0.001 compared to control group; **** – p<0.0001 compared to control group (Kruskal-Wallis rank analysis and the Dunn post-test); data shown as the mean ±SEM.

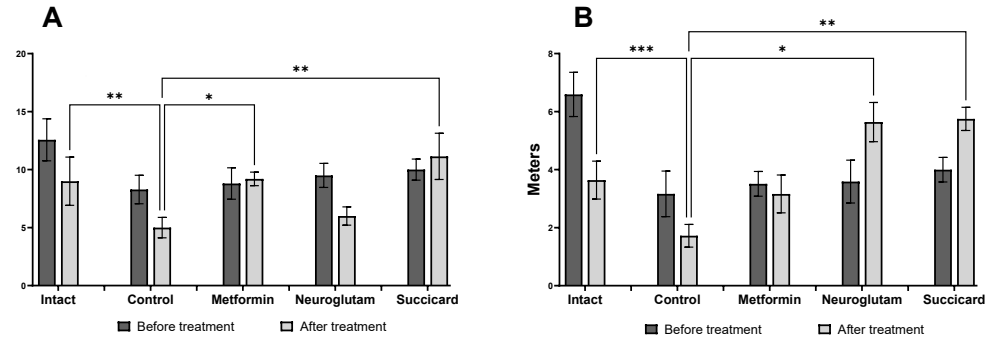


Figure 2. Exploratory activity (**A**) and spontaneous motor activity (**B**). ***Note:*** Significance is shown only for post-treatment groups; * – p<0.05 compared to control group; ** – p<0.01 compared to control group; *** – p<0.001 compared to control group (Kruskal-Wallis rank analysis and the Dunn post-test); data shown as the mean ±SEM.

In the elevated plus maze test, the succicard group showed a statistically significant increase in the number of entries into the open arms compared to the control group by 79%, indicating a reduction in anxiety-like behavior (Fig. 3). Simultaneously, in the metformin and succicard groups, a significant decrease in the number of entries into the closed arms was observed, reflecting a reduced need for a safe, enclosed space. An important indicator was also the statistically significant decrease in time spent on the central platform in the metformin, neuroglutam, and succicard groups compared to the control group, which is interpreted as a reduction in the conflict between exploratory drive and the sense of security. Moreover, animals in the metformin and succicard groups spent more time in the open arms of the apparatus than

control group animals. The obtained results demonstrate that all investigated drugs possess a pronounced anxiolytic effect, with metformin and succicard showing the most comprehensive effect.

In the novel object recognition test, the discrimination index indicators of diabetic animals differed slightly from those of intact animals; however, after the course of therapy, the control group's indicator significantly decreased (Fig. 4). In the group of animals receiving neuroglutam, a statistically significant increase in the discrimination index compared to the diabetes control group by 72% was recorded. This result indicates a significant improvement in short-term memory and the ability for differential object recognition in animals receiving neuroglutam.

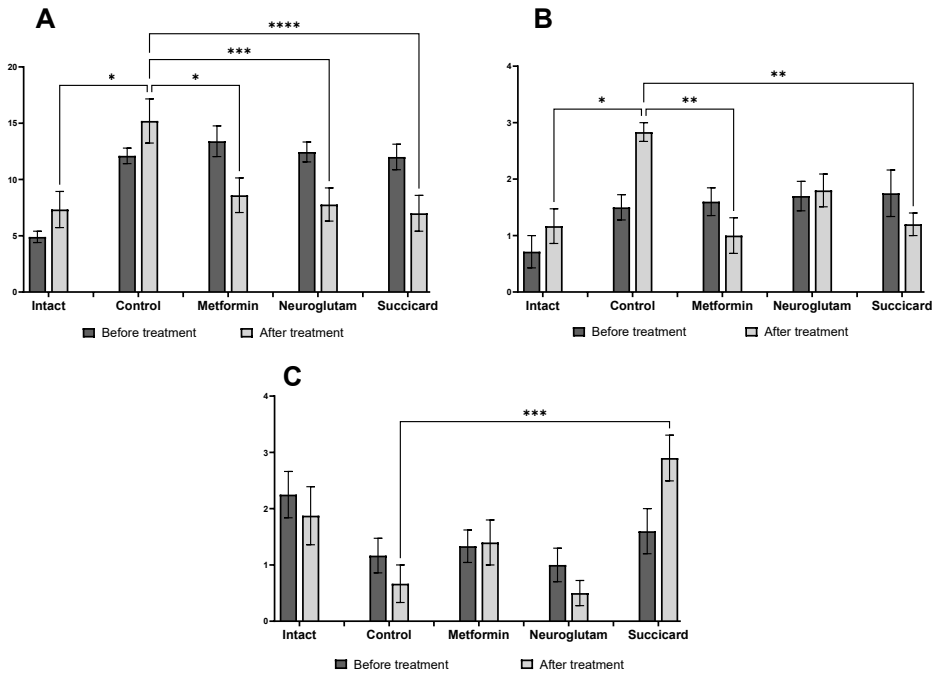


Figure 3. Time spent on the central platform (**A**); entries into the closed arms (**B**); entries into the open arms (C). ***Note:*** Significance is shown only for post-treatment groups; * – p<0.05 compared to control group; ** – p<0.01 compared to control group; *** – p<0.001 compared to control group (Kruskal-Wallis rank analysis and the Dunn post-test); data shown as the mean ±SEM.

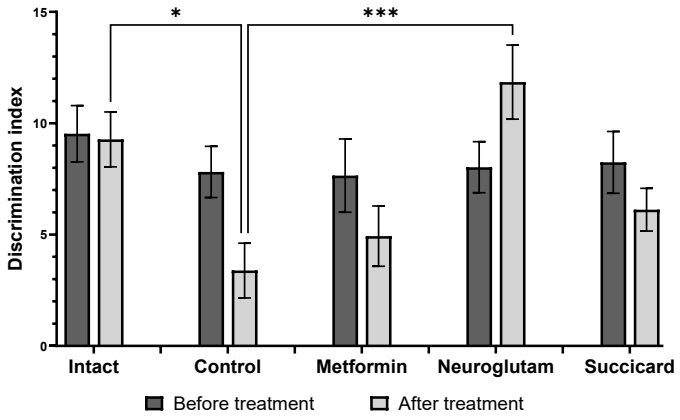


Figure 4. Results of the novel object recognition test before and after therapy. ***Note:*** Significance is shown only for post-treatment groups; * – p<0.05 compared to control group; *** – p<0.001 compared to control group (Kruskal-Wallis rank analysis and the Dunn post-test); data shown as the mean ±SEM.

The conducted Rotarod test revealed significant decreases in motor coordination and muscular endurance in diabetic animals compared to intact animals (Fig. 5). After the course of therapy, statistical analysis demonstrated that the groups receiving metformin and neuroglutam showed a significantly increased mean retention time on the rotating rod compared to the

diabetes control group ($p < 0.05$). The improvement in motor functions in these groups may be explained by metformin's ability to improve energy metabolism in muscle tissue through AMPK activation, as well as the neuroprotective properties of neuroglutam mediated by its influence on GABAergic systems. The obtained results indicate a positive effect of metformin and neuroglutam on sensorimotor functions impaired under conditions of accelerated aging against a diabetic state.

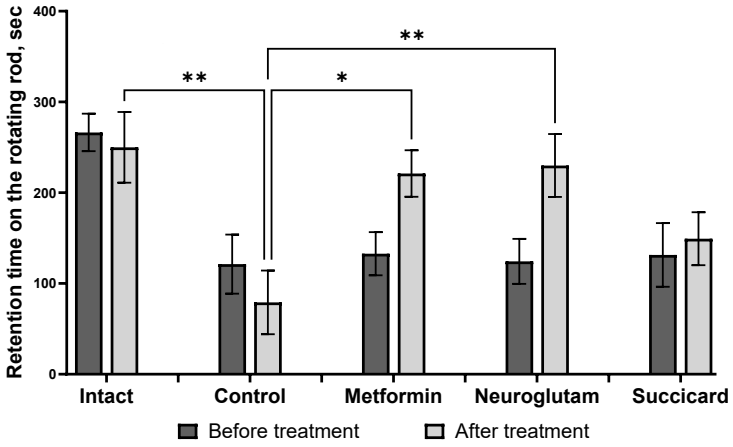


Figure 5. Retention time on the rotating rod before and after therapy. ***Note:*** Significance is shown only for post-treatment groups; * – $p<0.05$ compared to control group; ** – $p<0.01$ compared to control group (Kruskal-Wallis rank analysis and the Dunn post-test); data shown as the mean ±SEM; sec – seconds.

In the forced swimming with a load test, after the course of therapy, a statistically significant increase in the mean active swimming time compared to the diabetes control group was recorded only in the neuroglutam group (Fig. 6). In the metformin group, a trend towards increased swimming time was observed, but the differences with the control group did not reach the level of statistical significance. In the succicard group, the swimming time indicators practically did not differ from the control group and showed no dynamics compared to baseline measurements before treatment. The absence of a significant effect of succicard in this test, as well as in the Rotarod test, despite its efficacy in other behavioral tests, may indicate the selectivity of its action primarily on cognitive functions rather than physical endurance.

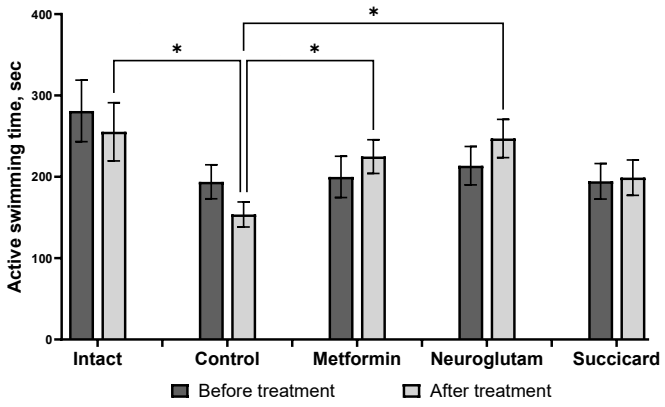


Figure 6. Results of the forced swimming with a load test before and after therapy. ***Note:*** Significance is shown only for post-treatment groups; * – $p<0.05$ compared to control group (Kruskal-Wallis rank analysis and the Dunn post-test); data shown as the mean ±SEM; sec – seconds.

Enzyme-linked immunosorbent assay of serum Klotho protein concentration revealed significant changes in this aging biomarker during the experiment (Fig. 7). Before the start of therapy, the Klotho protein level in the intact group did not statistically significantly exceed the indicators of the diabetes control group. After the course of treatment, an expected age-dependent decrease in Klotho level was recorded in the intact group. A statistically significant increase in Klotho protein level compared to the control group was detected in the metformin and succicard groups, indicating their geroprotective potential. In the neuroglutam group, the Klotho protein

concentration did not decrease after the course of therapy and was higher than the control group indicator. The obtained results demonstrate that metformin, neuroglutam, and succicard have the ability to counteract the decrease in Klotho protein level associated with accelerated aging in diabetes, which is consistent with the improvement in metabolic and behavioral indicators in these groups.

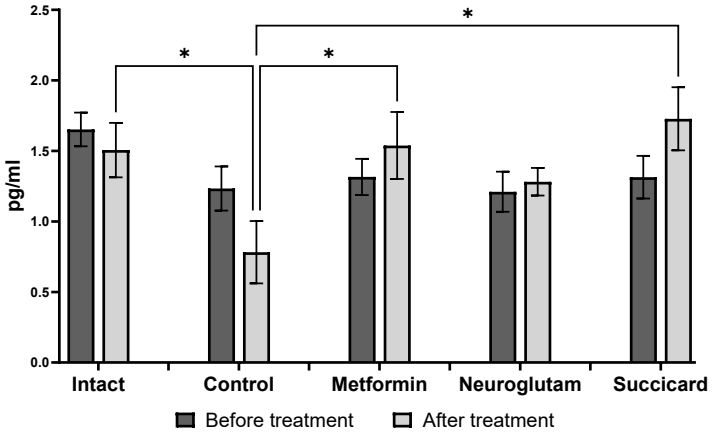


Figure 7. Enzyme-linked immunosorbent assay of serum Klotho protein concentration before and after therapy. ***Note:*** Significance is shown only for post-treatment groups; * – $p<0.05$ compared to control group (Kruskal-Wallis rank analysis and the Dunn post-test); data shown as the mean ±SEM.

Based on the study results, the ability of metformin not only to improve glucose tolerance indicators but also to increase Klotho protein levels was demonstrated, consistent with data on its geroprotective properties and ability to elevate Klotho protein levels. Neuroglutam demonstrated pronounced hypoglycemic, nootropic, and anxiolytic effects, which may be associated with its ability to modulate not only the glutamatergic system but also the GABAergic system, as well as its general polyvalent action, consistent with literature data. In the succicard group, a correlation was observed between the improvement in metabolic parameters (glycemia) and behavioral indicators, emphasizing the relationship between metabolic disorders and accelerated CNS aging. Furthermore, it is important to note its positive effect on Klotho protein levels, which may also indicate the presence of geroprotective properties.

Conclusion

The conducted study demonstrates that a long-term diabetic state, modeled using streptozotocin and nicotinamide, leads to the development of a complex of behavioral and metabolic impairments characteristic of accelerated aging. Metabolic disorders manifested as impaired glucose utilization and decreased serum Klotho protein concentration. In diabetic animals, a significant increase in anxiety in the elevated cross maze test, a decrease in overall exploratory activity, and reduced motor coordination and physical endurance were reliably recorded.

After 4 weeks of daily treatment with the substances, Metformin (400 mg/kg) and Succicard (50 mg/kg) demonstrated the most comprehensive action, significantly improving glucose tolerance, reducing anxiety, improving cognitive functions, and increasing Klotho protein levels. Neuroglutam (26 mg/kg) showed pronounced efficacy, significantly improving cognitive and motor functions, increasing physical endurance, and also demonstrating a trend towards normalization of glycemia and Klotho protein concentration. The obtained results allow considering GABA derivatives as promising agents for correcting various manifestations of accelerated aging associated with metabolic disorders.

Additional Information

Conflict of interest

The authors declare that they have no conflicts of interest.

Funding

The authors have no funding to report.

Ethics statement

The study design and protocol were approved by the Local Ethical Committee of Volgograd State Medical University, Minutes No. 2025/024 dated March 28, 2025 (registration number IRB 00005839 IORG 0004900 [OHRP]).

Acknowledgments

The authors have no support to report.

Data availability

All of the data that support the findings of this study are available in the main text.

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Author Contribution

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