EFFECT OF A TRIAZOLE DERIVATIVE ON MITOCHONDRIAL LIVER DYSFUNCTION IN ALLOXAN DIABETES

Sobirova Gulruh Khasan kizi[1], [2]Pozilov Mamurjon Komiljonovich
[1]Ferghana state university
[2]National University of Uzbekistan named after M.Ulugbek
https://doi.org/10.5281/zenodo.7984919

Abstract. *In recent years, the use of herbal preparations in the treatment of diseases has been growing significantly, which is explained by their therapeutic effectiveness and low negative effects on the body. Medicinal substances obtained on the basis of plant compounds are of great importance in medical practice, they are characterized by high physiological activity and pharmacological effects. Creation of effective antidiabetic drugs from bioactive compounds isolated from plants is one of the urgent problems in the future.*

Keywords: *ATP-Adenosine triphosphate, PTP–mitochondrial permeability transition pore (юқори ўтказувчанлик пораси), GLUT - glucose transporter.*

Today, in the treatment of diabetes and the creation of new effective drugs, much attention is paid to the fundamental knowledge of the pathogenesis of this disease, as well as the mechanisms of action of biologically active substances. During the development of experimental diabetes, the energy metabolism of cells is derailed, the generation of ATP in mitochondria is reduced, and energy deficiency in tissues has been determined. Such a strategy involves the identification of hypoglycemic compounds, the correction of their disorders at the level of mitochondria, and the development of new effective methods of prevention and treatment of diabetes.

During the development of various pathologies (diabetes, hepatitis, ischemia, etc.) along with changes in the physiological processes occurring in the cell, the functional state of mitochondria is disturbed. Mitochondrial function is essential for the vital activity of every cell. In diabetes mellitus, along with disruption of the GLUT and insulin signaling pathways of the cell membrane, there are also disturbances in the mitochondrial energetics and ion transport system. Therefore, it is important to study the changes occurring in the liver in addition to the degenerative changes occurring in β-cells of the pancreas in experimental diabetes. However, the mechanisms of correcting mitochondrial disorders with bioactive substances in diabetic conditions have not been sufficiently studied so far. Studying the synthesis of adenine nucleotides in the mitochondria, which are the energy source of the cell, and the status of ion channels, is very important in elucidating the mechanisms of diabetes. For this purpose, in this study, the effect of triazole derivative on the functional activity of the high-permeability pore (PTP-mitochondrial permeability transition pore) of rat liver mitochondria under conditions of alloxan diabetes was compared with rutin flavonoid.

Research methodology. Alloxan monohydrate was used to induce a diabetes model in animals. Laboratory animals were divided into IV groups. Here I group – control (n=4), II group – alloxan diabetes (n=4), III group – alloxan diabetes+triazole derivative (n=4) ва IV group alloxan diabetes + rutin (n=4). II, III and IV groups in order to induce diabetes in laboratory animals, after one day of starvation, a solution of alloxan 150 mg/kg (5% in 0.2 ml of dis. water) [Agzamov Kh.,

1983] was injected into the subcutaneous area of the abdominal cavity. Alloxan diabetic rats were blood sampled every 3 days and glucose levels were determined. 12 days after the injection of alloxan into rats, after the level of glucose in the blood exceeded 11 mmol/l, 0.2 ml of 0.9% NaCl solution was administered once a day to the animals of group II, and to group III of the experiment, the research substance - triazole derivative 10 mg/kg of rutin 20 mg/kg flavonoid was administered orally *(per. os)* once a day for 10 days to IV group. Studies were conducted after the blood glucose level decreased to 11 mmol/l.

Rat liver mitochondria were isolated using W.C.Schneider method of differential centrifugation. Kinetics of mitochondrial swelling was determined by spectrophotometer (spectrophotometer V-5000) by changes in optical density at 540 nm in an open cell (capacity 3 ml) with constant stirring of its suspension at 26°C. The following incubation medium (IM) was used to determine mitochondrial PTP permeability: 200 mM sucrose, 20 μM EGTA, 5 mM succinate, 2 μM rotenone, 1 μg/ml oligomycin, 20 mM Tris, 20 mM HEPES, and 1 мМ KH_2PO_4, pH 7,4 [He L., 2003].

Results. Antioxidant and antiradical properties of flavonoid compounds are very strong and can neutralize free radicals generated in pathological processes. Flavonoid compounds increase the synthesis of ATP, increase resistance to insulin resistance and restore mitochondrial dysfunction in diabetic conditions. The antidiabetic activities of flavonoid compounds have been extensively studied, but the hypoglycemic properties of triazole derivatives and their effects on mitochondrial functional changes have not yet been fully investigated. For this purpose, the effect of triazole derivatives on mPTP process of rat liver mitochondria was studied comparatively with rutin flavonoid. Initially, in our experiment, experiments were carried out on the effect of hypolatin-8-glucoside flavonoid on the contraction of rat liver mitochondria in the presence of $CaCl_2$ under conditions of alloxan diabetes. In the presence of a coconcentration of 20 μM of $CaCl_2$ in the incubation medium, the mitochondrial staining was taken as a control (100%).

According to the obtained results, it was noted that the number of mitochondria isolated from rat liver increased by 81.8% in alloxan diabetes compared to control (group I). As a result of administration of triazole derivative (perally once a day for 10 days) to group III animals with alloxan diabetes, it was found that the glucose level in their blood decreased to a normal level, and it was found that the inhibition of mitochondria isolated from the liver with the presence of Ca^{2+} ions was inhibited by 58.7% compared to alloxan diabetes. As a result of administration of anti-diabetic compound rutin flavonoid to group IV animals with alloxan diabetes, it was found that the inhibition of liver mitochondria with Ca^{2+} ions was inhibited by 45.5% compared to alloxan diabetes.

The obtained results indicate that in alloxan diabetes, the conformation of rat liver mitochondria PTP in a highly conductive state may be the mechanism of disruption of cell and mitochondrial ion homeostasis and reduction of ATP synthesis. Thus, alloxan, a triazole derivative with hypoglycemic activity, inhibits mPTP permeabilization by reducing mitochondrial damage in diabetic conditions. In future experiments, it is necessary to study the effect of this bioactive substance alloxan on other functional parameters of mitochondria in diabetic conditions.

REFERENCES

1. Агзамов Х., Алматов К.Т., Рахимов М.М., Туракулов Я.Х. Функционирование митохондрий печени при аллоксановам диабете // Вопросы мед. химии. –1983. - Т.29. – №1.– С. 61-65.
2. He L., Lemasters J.J. Heat shock suppresses the permeability transition in rat liver mitochondria // J. Biol. Chem. – 2003. – V. 278(19). – P. 16755-16760.
3. Позилов М.К., Эргашев Н.А., Асраров М.И., Эшбакова К.А. Сальвифолин дитерпеноидининг жигар митохондрияси нафас олиши ва оксидланишли фосфорланишга таъсири // Инфекция иммунитет и фармакология журнали. – 2015.- №1. – 127-134 Б.
4. Позилов М.К., Эргашев Н.А., Эшбакова К.А., Асраров М.И. Сальвифолин дитепеноидининг каламуш жигари митохондриялари циклоспорин сезгир порасига таъсири // “ЎзМУ хабарлари” илмий журнали. - 2013.- №4/2. – Б. 72-73.
5. Позилов М.К., Эрназаров З.М., Куканова Н.Ф., Асраров М.И., Махмудов Р.Р. Госситан полифенолининг юрак митохондрияси ион каналларига таъсири // – Тошкент тиббиёт академияси ахборотномаси. – 2019. – № 3.– С. 64-67.
6. Позилов М.К., Асраров М.И., Абдуллажанова Н.Г. Мавлянов С.М. Действие полифенола госситана на мембранные процессы митохондрий печени крыс // ЎзМУ хабарлари. – 2018. – №3/1. – С. 203-207.
7. Позилов М.К., Эргашев Н.А., Асраров М.И., Рахматуллаева М.М., Аминов С.Н. Гликоразмулиннинг митохондрия нафас олиши ва оксидланишли фосфорланишига таъсири // Фармацевтика журнали. – 2014. – №2. – Б.94-98
8. Юнусов, М. М., Сабирова, Г. Х., & Хабибуллаев, Ф. Н. (2022). ПРОБЛЕМА ЗДОРОВЬЯ В ВОСПИТАНИИ ДЕТЕЙ. *Science and innovation*, *1*(D3), 89-90.
9. Юнусов, М. М., Сабирова, Г. Х., & Абдурахимов, И. Н. У. (2022). ИНФЕКЦИОННЫЕ ЗАБОЛЕВАНИЯ И ИХ ПРОФИЛАКТИКА. *Science and innovation*, *1*(D3), 87-88.
10. Собирова, Г. Х., & Умурзакова, Ф. (2022). РАСТЕНИЕ ФИЗАЛИС И ЕГО ЛЕЧЕБНЫЕ СВОЙСТВА. *O'ZBEKISTONDA FANLARARO INNOVATSIYALAR VA ILMIY TADQIQOTLAR JURNALI*, *1*(12), 86-89.
11. Собирова, Г. Х. ОПРЕДЕЛЕНИЕ АНТИОКСИДАНТНОЙ АКТИВНОСТИ ЭКСТРАКТОВ ШИПОВНИКА, ПУСТЫРНИКА И БОЯРЫШНИКА. *RESEARCH AND EDUCATION* 1.7 (2022): 114-122.
12. Собирова, Г. Х. АНТИРАДИКАЛЬНАЯ АКТИВНОСТ ЭКСТРАКТОВ ПУСТЫРНИКА, ШИПОВНИКА И БОЯРЫШНИКА. *Oriental renaissance: Innovative, educational, natural and social sciences* 2.11 (2022): 130-136
13. Собирова, Г. Х. БИОЛОГИЧЕСКАЯ АКТИВНОСТЬ ЭКСТРАКТОВ БОЯРЫШНИКА, ШИПОВНИКА И ПУСТЫРНИКА. *Journal of Integrated Education and Research* 1.5 (2022): 160-164.