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The Influence of Diazamino Derivatives of Gossypol on ATP-Sensetive Potassium Channel Activity of Rat Liver Mitochondria in Streptozotocin Diabetes

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Abstract This research article describes the effect of water-soluble complexes of diazoimine derivatives of gossypol YAN-2 (4:1) and YAN-2 (6:1) on the activity of ATP-dependent potassium channels in the liver mitochondria of rats with streptozotocin (STZ) diabetes on *in vivo* experiment. Mitochondria of purebred white rats were isolated by differential centrifugation. Diazoimine derivatives of gossypol YAN-2 (4:1) and YAN-2 (6:1) and the flavonoid quercetin at a dose of 30 mg/kg were administered orally for 10 days to rats with STZ diabetes. According to the research the diazoimine derivatives of gossypol YAN-2 (4:1) and YAN-2 (6:1) enhance the inhibitory activity of the mitoK_{ATP} channel in the liver of rats with STZ diabetes. The readily available hypoglycemic compound quercetin has also been found to increase mitoK_{ATP} channel activity in the liver of STZ-diabetic rats. Recent studies on quercetin have shown that quercetin reduces the risk of cardiovascular disease and liver disease by reducing hyperglycemia, high blood pressure, hyperlipidemia, and promoting weight loss.

Keywords Diabet, Mitochondria, STZ, Quercitin, Liver

1. Introduction

Many pharmacological agents used in the treatment of diabetes and other diseases have recently been shown to affect mitochondria. Depending on the biological properties of the pharmacological agents and the specific research directions, this effect can be positive or negative, direct or indirect. Some modulators have been specifically designed to target mitochondria [1]. Some modulators can act as activators or inhibitors of mitoK_{ATP} channel which is located in the inner mitochondrial membrane. For example, glibenclamide, an inhibitor of the cytoK_{ATP} channel of the pancreatic plasma membrane, inhibits the ATP-sensetive potassium channel, contributing to membrane depolarization. Bioactive compounds isolated from plants can restore mitochondrial dysfunction and actively participate in the flow of potassium ions. Such antidiabetic drugs may be a promising approach for the development of new tools for drug therapy of diabetes. Although many antidiabetic drugs (metformin) are widely prescribed in diabetes mellitus, their molecular mechanisms of action are still controversial [1,2]. In this context, the aim of this work is to investigate the effects of some polyphenolic compounds on liver mitochondrial dysfunction in streptozotocin (STZ) diabetes.

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2. Materials and Methods

The compounds YAN-2 (4:1) and YAN-2 (6:1) were presented by scientists from the Institute of Bioorganic Chemistry. To a 50% solution of glycyrrhizic acid monoammonium salt (GKMAT) in ethyl alcohol, an alcohol solution of the diazoimino derivative of gossypol in the corresponding molar ratio was added and the mixture was stirred for 4-5 hours at room temperature. The organic solvent of the mixture was evaporated in a rotary evaporator at a temperature of 50℃, and the aqueous part was dried in a lyophilizer. YAN-2 is a diazoimino derivative of gossypol. YAN-2 in ratios of 4:1 and 6:1, of which the content of GCMAT in the ratio of 1 and diazoimino derivative of gossypol in ratios of 6 and 4 are water-soluble complexes. For the experiment, the existing hypoglycemic compound quercetin was used as a standard prototype.

The experiments were conducted on inbred white rats weighing 180-200 g. Scientific research on experimental animals was carried out in accordance with the international Declaration of Helsinki, the Council for International Organizations of Medical Sciences (CIOMS; the Council for International Organizations of Medical Sciences) (1985), and the “Bioethical Code for the Use of Laboratory Animals

in Scientific Research" (2019) of the Institute of Biophysics and Biochemistry. Mitochondria from rat liver were isolated using the W.C. Schneider method of differential centrifugation. The experimental animals were divided into groups: group I - healthy, group II - STZ-diabetes, group III - STZ-diabetes + YAN-2 (6:1), group IV STZ diabetes + YAN-2 (4:1) and group V (STZ diabetes + quercetin). To induce diabetes in rats of groups II, III, IV and V, after a one-day fast, a solution of STZ 50 mg / kg (0.1 mol / l citrate buffer, 0.2 ml, pH 4.5) was injected subcutaneously into the abdominal cavity. Blood was taken from animals with STZ-diabetes every 3 days and glucose levels were determined. After the blood glucose level in rats exceeded 11 mmol/l after injection of STZ (12 days), animals of group II were administered 0.2 ml of 0.9% NaCl solution once a day, group III of the experiment received 30 mg/kg of the YAN-2 (6:1) complex, group IV received 30 mg/kg of the YAN-2 (4:1) complex, and group V received 30 mg/kg of the flavonoid quercetin once a day for 10 days. The effects of YAN-2 (6:1), YAN-2 (4:1), and quercetin on the activity of the ATP-dependent potassium channel of liver mitochondria in animals with STZ diabetes (when the blood glucose level decreased to 11 mmol/l) were determined. The blood glucose level was determined using the glucose oxidase method.

Permeability of mitoK$_{ATP}$ channel (0.3-0.4 mg/ml protein) was determined in 3 ml cells by measuring the change in optical density at a wavelength of 540 nm using a spectrophotometer (V-5000) [3].

Statistical analysis of the obtained results was carried out using the Origin 8.6 (USA) computer program. The results were presented in the form of calculating the arithmetic mean of 5 experimental samples.

3. Results and Their Analyses

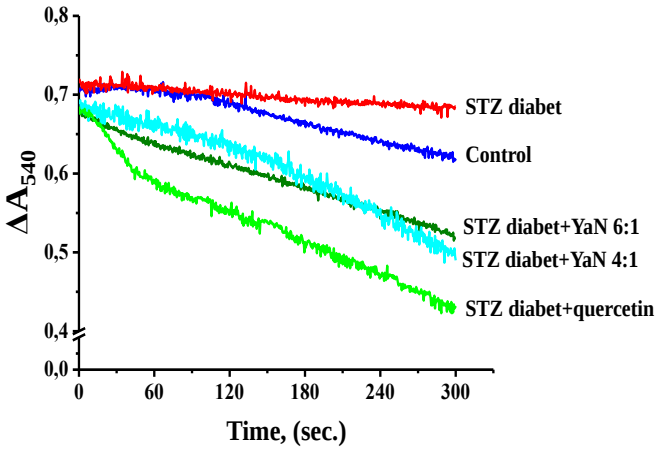

Figure 1. Comparative study of the effect of water-soluble YaN 6:1 and YaN 4:1 supramolecular complexes of gossypol diazamino derivatives on rat liver mitoK$_{ATP}$ channel activity under conditions of STZ diabetes with quercetin. Original image taken on a spectrophotometer

The effect of diazamino derivatives of gossypol polyphenol on mitoK$_{ATP}$-channel activity of liver mitochondria membrane of STZ diabetic rats was studied. Determination of the permeability of the mitoK$_{ATP}$-channel of the rat liver is based on the fact that the suspension of mitochondria scatters the light passing through it, as a result of which the outgoing light intensity decreases from the incoming intensity. Mitochondrial permeability was determined in a spectrophotometer based on changes in optical density at a wavelength of 540 nm (Figure 1).

In experiments to inhibit the activity of the liver mitoK$_{ATP}$ channel under STZ diabetes conditions, ATP was used at a concentration of 200 μM ATP.

According to the results obtained, the permeability of the liver mitoK$_{ATP}$ channel of healthy rats of group I taken for the experiment was 0.84 $\Delta A_{540} \times 10$ min optical density, with almost no significant changes. The permeability of the liver mitochondria of group II rats with STZ diabetes was (0.30 $\Delta A_{540} \times 10$ min), which was inhibited by 64.3% compared to the control (healthy group I). Thus, the activity of the mitoKATP channel of rat liver mitochondria was inhibited under conditions of STZ diabetes. Inhibition of the liver mitoK$_{ATP}$ channel in STZ diabetes indicates that their uniport transport of potassium ions is reduced. In our next experiment, rats of group III with STZ diabetes were treated with a 6:1 diazamino derivative of gossypol at a dose of 30 mg/kg for 10 days. After the blood glucose level of the rats of the STZ diabetes group taken for the experiment approached the control group, the rats were decapitated. According to the results, it was found that the liver mitoKATP channel (1.59 $\Delta A_{540} \times 10$ min) of rats of group III with STZ diabetes was activated 5.3 times compared to the indicators of group II with STZ diabetes (Figure 2).

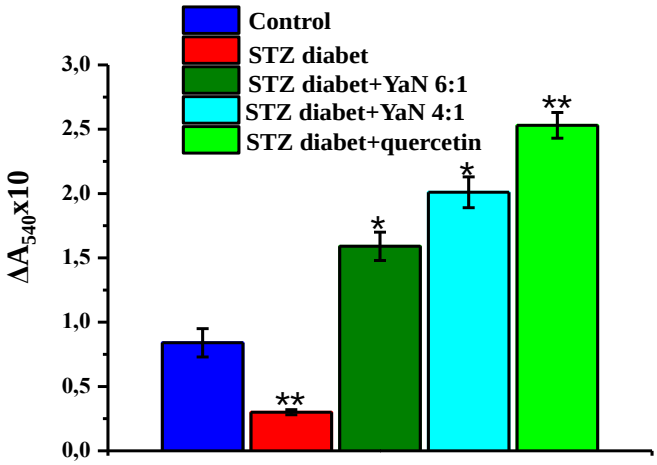

Figure 2. Comparative study of the effect of water-soluble YaN 6:1 and YaN 4:1 supramolecular complexes of gossypol diazamino derivatives on rat liver mitoK$_{ATP}$ channel activity under conditions of STZ diabetes with quercetin. (*P<0,05; **P<0,01; n=5)

Thus, it was found that the diazamino derivative of gossypol, called YaN 6:1 GMAT, activates the inhibitory state of the mitoKATP channel located in the membrane of liver mitochondria in conditions of STZ diabetes. The activation of the liver mitoK$_{ATP}$ channel permeability under the influence of the diazamino derivative of gossypol YaN

6:1 GMAT indicates its participation in the potassium ion cycle in mitochondria.

Continuing the experiments, the effect of the YaN 4:1 GMAT diazamino derivative on the activity of the mitoK_{ATP} channel of liver mitochondria under conditions of STZ diabetes was also investigated. Rats of group IV with STZ diabetes were treated with YaN 4:1 diazamino derivative of gossypol at a dose of 30 mg/kg for 10 days. According to the results obtained, the liver mitoCATF channel of group IV rats with STZ diabetes was activated 6.7% (2.01 $\Delta A_{540} \times 10$ min) compared to the indicators of group II with STZ diabetes (Figure 2). Thus, the YaN 4:1 diazamino derivative of gossypol increased the activity of the rat liver mitoK_{ATP} channel under conditions of STZ diabetes. This polyphenol compound was also found to reduce the amount of glucose in the blood [4] and increase the activity of the liver mitoK_{ATP} channel under conditions of STZ diabetes. It was found that the increase in hepatic mitoK_{ATP} channel activity under the influence of the YaN 4:1 diazamino derivative of gossypol under conditions of STZ diabetes was more active than the YaN 6:1 derivative of gossypol. From this it can be concluded that the YaN 4:1 diazamino derivative of gossypol was involved in the homeostasis of potassium ions in the matrix by increasing the uniport transport of potassium ions through the hepatic mitoK_{ATP} channel, the permeability of which was inhibited under conditions of STZ diabetes.

The available hypoglycemic compound quercetin, which was used for the experiment, was also found to increase the activity of the mitoK_{ATP} channel in the rat liver under conditions of STZ diabetes. In this case, the permeability of the mitoK_{ATP} channel of the liver mitochondria of group V rats, which were treated by pharmacological therapy with quercetin (30 mg/kg for 10 days), was found to increase by 8.4 times compared to the indicators of group II. Thus, the flavonoid quercetin increased the permeability of potassium ions in rat liver mitochondria under conditions of STZ diabetes. In addition, it was found that quercetin was slightly more active than the YaN 6:1 and YaN 4:1 derivatives of gossypol in increasing the activity of the mitoK_{ATP} channel located in the inner membrane of liver mitochondria under conditions of STZ diabetes. This property of quercetin is explained by its broad-spectrum antidiabetic effect. Recent studies with quercetin have shown that quercetin reduces the risk of cardiovascular and liver diseases by reducing hyperglycemia, high blood pressure, hyperlipidemia, and aiding weight loss. Some studies have shown that this flavonoid is beneficial in chronic hypertension, dyslipidemia, obesity, and type 2 diabetes [5]. Quercetin lowers blood glucose levels, liver glycogen levels and enzyme levels, and cholesterol levels [5,6]. In addition, it has been shown to prevent oxidative damage, enhance pancreatic β-cell renewal and subsequent insulin secretion [7]. Compared to current synthetic agents, which have many adverse effects, quercetin has been shown to be an excellent standard for the development of new antidiabetic drugs.

4. Conclusions

It was found that inhibition of hepatic mitoK_{ATP} channel permeability is activated by streptozotocin (STZ). The flavonoid quercetin, taken as a standard prototype, also increased the permeability of rat liver mitochondria for potassium ions under STZ-diabetic condition.

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