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MECHANISMS OF ACTION OF GLYCYRRETIC ACID AND ITS DERIVATIVES ON MITOCHONDRIAL MEMBRANES

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Abstract*. The article examines the effect of new synthetic derivatives of glycyrrhetic acid (GrA) on the functional parameters of mitochondria (Mx), as well as the parameters of the CsA-sensitive pore of Mx membranes. As a result of the studies, it was shown for the first time that the derivatives of GrK are 2-(N-cytisine)-ethyl-3-0-acetyl-18βH-glycyrrhetate (cytisine-ethyl-GC), 2-(N-cytisine)-isopropyl-3-0-acetyl-18βH-glycyrrhetate (cytisine-isopropyl-GC) and N-(2-pyridyl)-3-0-acetyl-11-ketoolean-12-ene-30-amide (2-pyridyl-GC -amide) inhibit the activity of the CsA-sensitive pore and have a protective effect on Mx membranes. At the same time, the damaging effect of Ca2+ ions and the lipid peroxidation process is reduced. Other derivatives of GrK- N-(4-pyridyl)-3-0-acetyl-11-ketooleane-12-en-30-amide (4-pyridyl-GC-amide) and Ca^{2+}(N-morpholine)-ethyl-3 -O-acetyl-18βH-glycyrrhetate (morpholine-GC) uncouples OF, enhances the damaging effect of CsA-sensitive pore inducers on membranes, increasing their permeability to cations.*

Keywords: *mitochondria (Mx), membrane permeability, CsA-sensitive pore, lipid peroxidation (LPO), oxidative phosphorylation (OP), antioxidants, pro-oxidants, free radicals, apoptosis, necrosis, glycyrrhetic acid derivatives.*

Literary data suggest that the Mx and CsA-sensitive pore are targets for the action of various biologically active substances, pathogens and pharmaceuticals [Kamburova, 2001; Salikhodzhaeva et al., 2002; Fioretal., 2004]. In this regard, recently, many laboratories around the world have been actively studying the mechanisms of regulation of the functional state of the Ca^{2+} dependent CsA-sensitive pore of Mx and other Ca2+-dependent intracellular processes by biologically active compounds [Salvietal., 2003]. To regulate the functional parameters and state of the CsA-sensitive pore, herbal preparations are often used, the biological and pharmacological activity of which is due to their membrane-active properties. Chemical modification of natural compounds can change their biological and pharmacological properties [Baltina et al., 1992;].

The study of the role of lipid peroxidation (LPO) in the regulation of the most important cell functions is of interest for a number of reasons. Induction of LPO in Mx leads to a change in membrane permeability, a decrease in membrane potential, uncoupling of OF and ATP hydrolysis. The influence of LPO on the functions of Mx is realized both at the level of the direct influence of LPO products on the lipid matrix of membranes, and various indirect effects.

One of the most important mechanisms through which LPO reactions can indirectly regulate the functions of Mx is the CsA-sensitive pore, the transition of which to an open state is considered as an essential stage of Mx damage during oxidative stress (OS) and associated necrosis or apoptosis. Free radicals are highly reactive compounds that can disrupt the structure and function of animal and plant cells. Organisms are constantly exposed to them. Firstly, they are constantly formed as a result of natural metabolic processes occurring in the cell. Secondly, free radicals are formed under the influence of external factors, both natural and anthropogenic or

technogenic (under the influence of a polluted environment, smoking, radiation, household chemicals).

It is known that free radicals are the main cause of the development of many diseases in humans and animals. The body also has an antioxidant system that protects the body from free radicals. Antioxidants are able to neutralize the activity of free radicals and protect phospholipids of cell membranes from oxidation.

The study of the regulatory effects of GrK derivatives at the level of Mx and CsA-sensitive pores will significantly expand the existing understanding of the mechanisms of action of bioactive compounds on Mx membranes. The results of this work can find application in medical practice in connection with various disorders of the functional parameters of Mx caused by changes in the state of the CsA-sensitive pore. The research conducted and the results obtained will allow us to develop new approaches and pharmaceuticals that can be used in the treatment of various liver pathologies.

Preparations from licorice root were used as medicines to treat various diseases [Tolstikov G.A., 1997].

Studies of the membrane-active properties of G3K have shown that it does not have antiradical activity, however, it stabilizes mitochondrial membranes (Mx), modifies the state of the CsA-sensitive pore of Mx, preventing its opening [Kamburova V.S. 2001. Beskina O.A.2000]

The search and creation of new highly effective drugs based on GzK and glycyrrhetic acids (GrA) by modifying certain functional groups are relevant for research practice. It is also of interest to study the relationship between the chemical structure and anti- and pro-oxidant properties of GRK derivatives. In this regard, we studied the effect of GrK and some of its derivatives (Fig. 1) on the process of lipid peroxidation of Mx membranes.

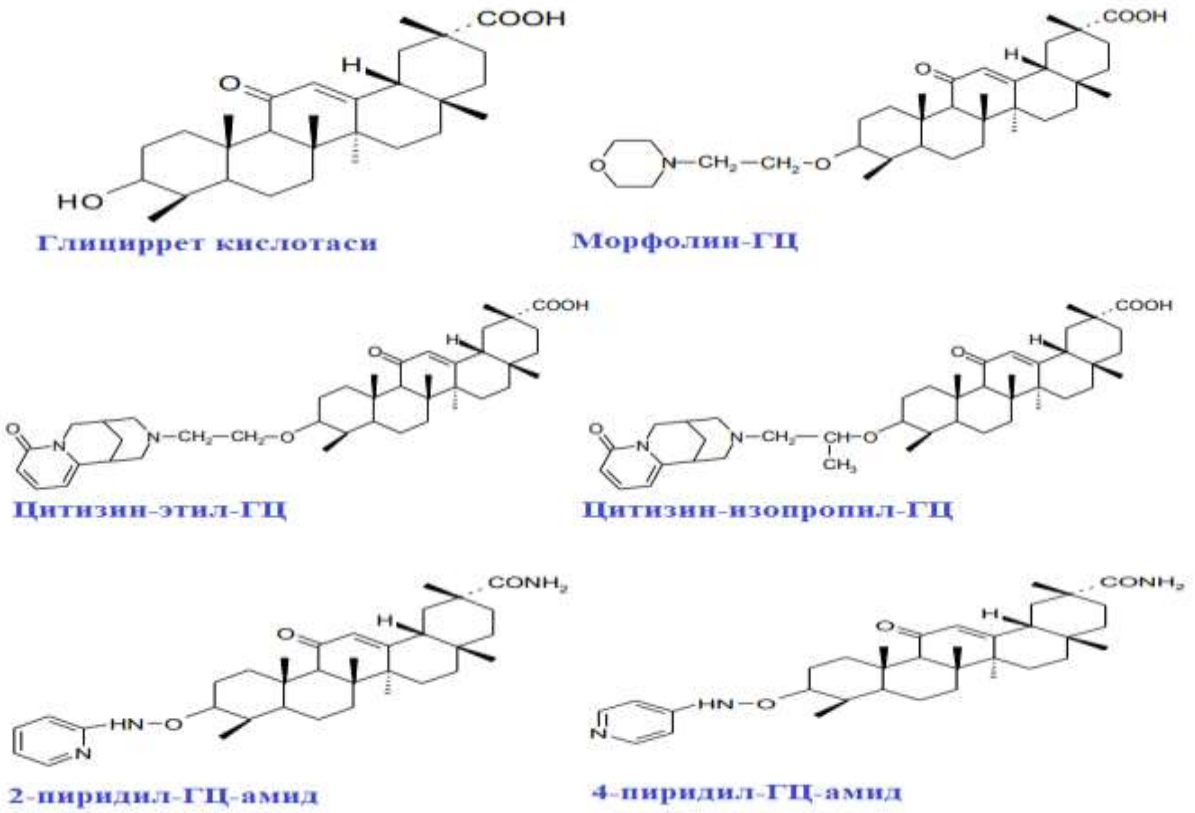


Figure. 1. Structural formulas of glycyrrhetic acid and its derivatives.

(List of abbreviations used: **GRC** - glycyrrhetic acid; **Cytisine**-ethyl-GC: 2-(N-cytisine)-**ethyl**-3-0-acetyl-18βH-glycyrrhetate; **Cytisine-isopropyl**-GC: 2-(N-cytisine)-isopropyl-3-0-acetyl-18□H-glycyrrhetate; **Morpholine**-GC: 2-(N-morpholine)-ethyl-3-0-acetyl-18βH-glycyrrhetate; 2-pyridyl-GC-amide: N-(2-pyridyl)-3-0-acetyl-11-ketoolean-12-ene-30-amide; 4-pyridyl-GC-amide: N-**(4-pyridyl)**-3-0-acetyl-11- ketoolean-12-ene-30-amide.)

Materials and methods. Mx was isolated from the liver of rats weighing 150-200 g. by differential centrifugation method. LPO was induced in the presence of FeSO4 (1x10-3M) and ascorbate (2x10-4M) or by the addition of 4 mM cumene hydroperoxide (CHP). The amount of malondialdehyde (MDA) formed was determined using the molar extinction coefficient (e=1.56.105 M -1 cm-1) [10].

Results and discussion. A natural question arises whether GRK derivatives, which convert the CsA-sensitive pore into a closed configuration, have antioxidant properties. In this regard, we studied the effect of GrK and its derivatives on the LPO process of Mx membranes. Cumene hydroperoxide (CHP) was used as a LPO inducer. As a result of the studies, it was found that GrK increases the accumulation of malondialdehyde (MDA) in Mx membranes by 40% (Fig. 2). Similar data were also obtained by other authors. The addition of other GPC derivatives - 2-pyridyl-GC-amide, cytisine-isopropyl-GC and cytisine-ethyl-GC at a concentration of 50 μM prevented the effect of GPC on the level of MDA in isolated liver Mx. At the same time, the decrease in MDA accumulation was 20%, 40% and 45%, respectively, relative to the control (Fig. 2).

Subsequently, we studied the effect of GrK derivatives on the LPO system induced by Fe^{2+} ascorbate (Fig. 2). Under these conditions, GC derivatives - 2-pyridyl-GC-amide, cytisine-isopropyl-GC and cytisine-ethyl-GC at a concentration of 50 μM prevented the effect of Fe^{2+} ascorbate on the level of MDA in isolated Mx by 15%, 30.6% and 50 %, respectively.

Thus, we have established that the derivatives of GrK: 2-pyridyl-GC-amide, cytisine-isopropyl-GC and cytisine-ethyl-GC have antioxidant properties and have a protective effect on Mx, reducing the damaging effect of GPC and the lipid peroxidation process.

As we noted earlier, one of the mechanisms through which there may be an indirect regulatory effect of LPO reactions on Mx functions is the CsA-sensitive pore. Perhaps this mechanism is influenced by biologically active compounds: 2-pyridyl-GC-amide, cytisine-isopropyl-GC and cytisine-ethyl-GC on mitochondrial functions.

We also studied the effect of other GrK derivatives on the LPO process of Mx membranes, using LPO inducers - HPA and the Fe^{2+} ascorbate system. When studying the effect of morpholine-GC, 4-pyridyl-GC-amide on the LPO of Mx membranes, it was shown that these derivatives acted on the state of the Mx pore, increasing the passive permeability of the membranes and reducing the Ca2+ capacity of Mx. Previous experiments with GrK showed that it increases the accumulation of MDA in Mx membranes. However, the effects of the compounds morpholine-GC and 4-pyridyl-GC-amide at a concentration of 50 μM are weaker than the classical LPO inducers - HPA and the Fe^{2+}–ascorbate system (Figure 2, Figure 3 and Figure 4). An increase in the concentration of drugs in the incubation medium led to a further increase in the accumulation of MDA in Mx membranes.

Experiments have shown that in the presence of HPA, an increase in the accumulation of MDA is observed. Against this background, preparations of morpholine-GC and 4-pyridyl-GC-amide (50 μM) led to a further increase in the accumulation of MDA in Mx membranes. Higher

concentrations of the drugs morpholine-GC and 4-pyridyl-GC-amide in SI led to a further increase in the accumulation of MDA in Mx membranes by 26% and 30%, respectively. The results obtained confirm our assumption that the compounds morpholine-GC and 4-pyridyl-GC-amide have pro-oxidant properties (Figure 3).

Similar results were also obtained with induction by the Fe^{2+}– ascorbate system (Fig. 3). Subsequently, we studied the effect of morpholine-GC and 4-pyridyl-GC-amide on the LPO system induced by Fe^{2+} ascorbate (Fig. 4 and Fig. 4). Under the same conditions, the drugs we tested at a concentration of 50 μM contributed to a further increase in the accumulation of MDA in Mx membranes by 30% and 37%, respectively.

It is known that one of the mechanisms of disruption of the CsA-sensitive pore is the intensification of lipid peroxidation against the background of a decrease in the activity of antioxidant enzymes - catalase and superoxide dismutase. As a result, desensitization of membranes and an increase in their permeability to various ions and substances is observed. Some compounds we studied reduced the level of MDA in membranes, which indicated their antioxidant properties.

Thus, 2-pyridyl-GC-amide, cytisine-isopropyl-GC and cytisine-ethyl-GC have antioxidant properties and have a protective effect on Mx, reducing the damaging effect of HPA and the Fe^{2+} ascorbate system, and other GC derivatives: morpholine-GC and 4-pyridyl-HC-amide have pro-oxidant properties, enhancing the damaging effect of HPA and the Fe^{2+}ascorbate system.

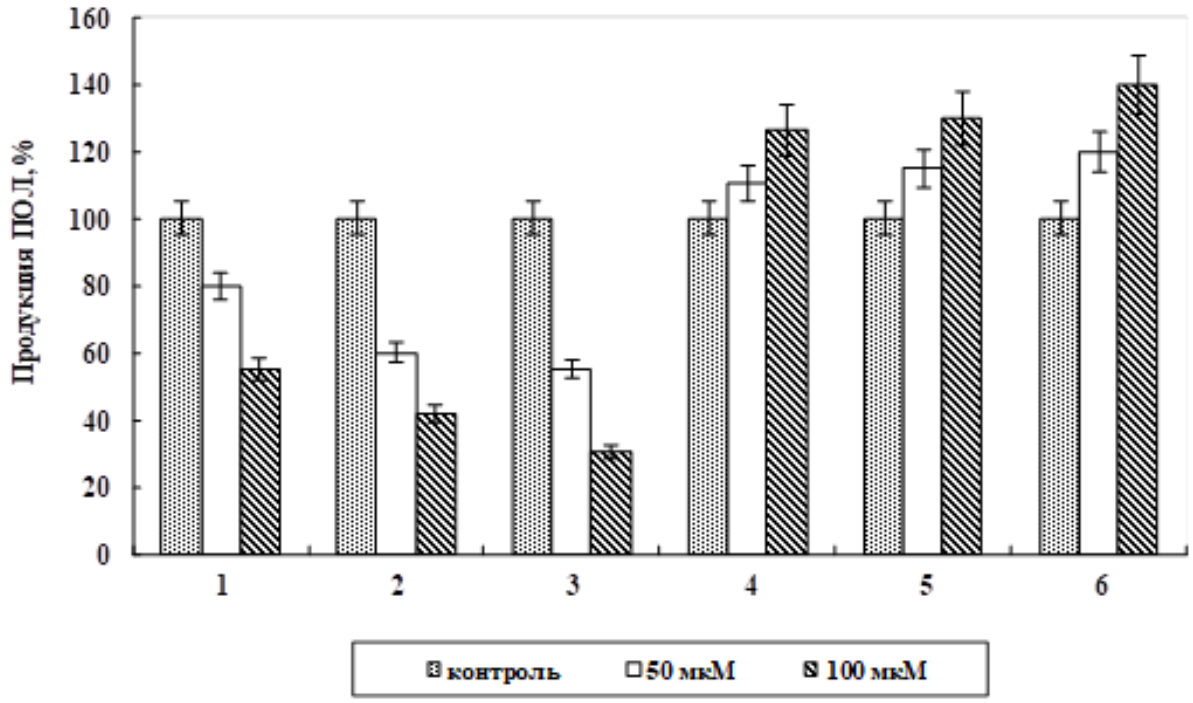
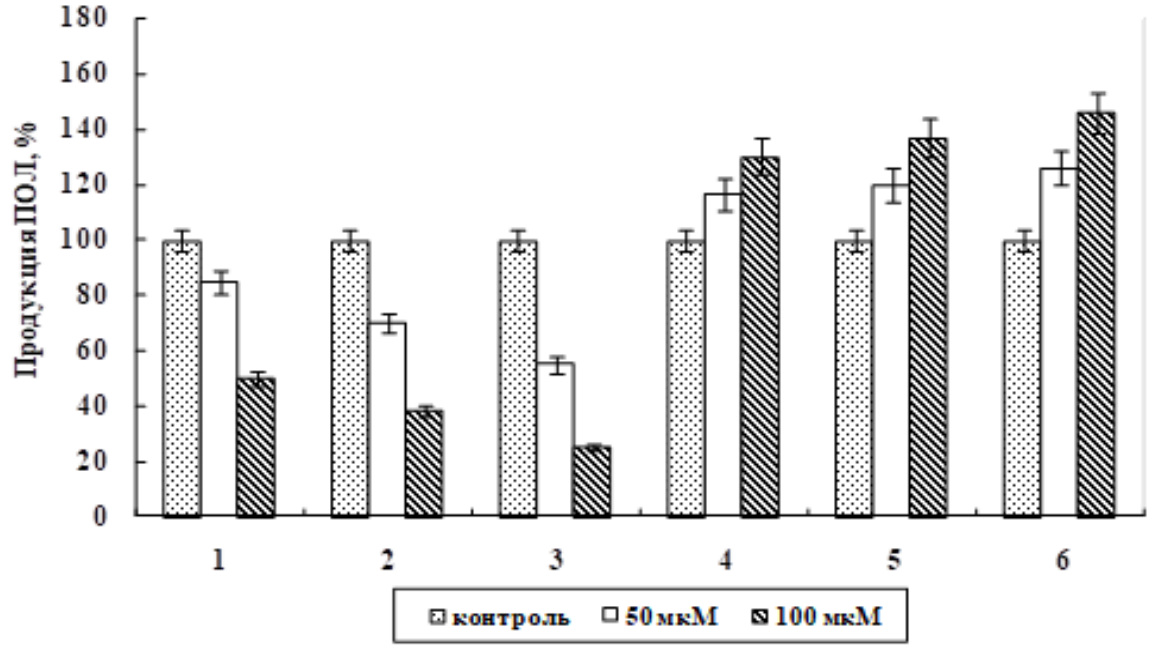


Figure 2. The influence of GRK acid derivatives on GPA-dependent lipid peroxidation

1. - 2-pyridyl-HC-amide; 2. - cytisine-isopropyl-HC; 3. - cytisine-ethyl-GC; 4. - 4-pyridyl-HC-amide; 5. - morpholine-GC; 6. - GrK. (n =6, P□0.05).



3 Figure. Effect of GRK acid derivatives on Fe-ascorbate

1. - 2-pyridyl-HC-amide; 2. - cytisine-isopropyl-HC; 3. - cytisine-ethyl-GC; 4. - 4-pyridyl-HC-amide; 5. - morpholine-GC; 6. - GrK. (n =6, P<0.05).

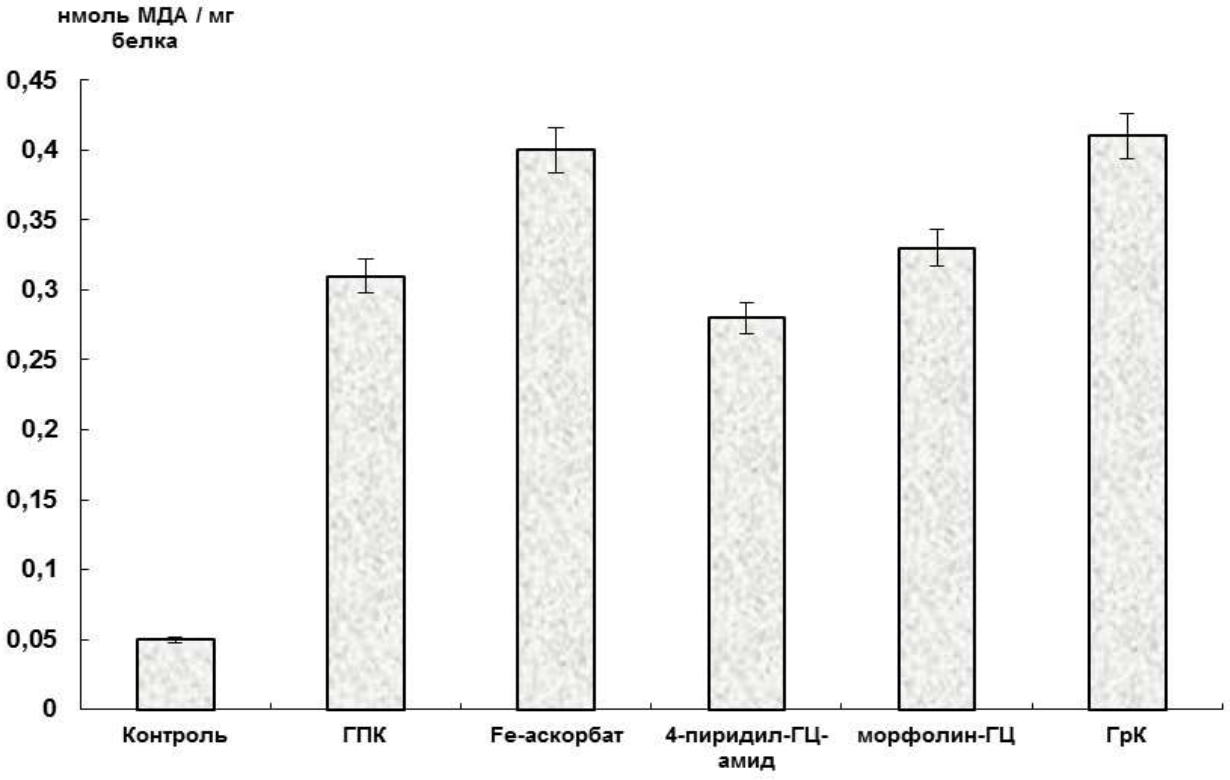


Figure 4. The influence of GrK derivatives - GrK morpholine-GC and* 4-pyridyl-HC-amide on the LPO system

Notes*. The concentration of GRK and its derivatives is 50 μM. (n =6, P<0.05).

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