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ASSESSMENT OF CARDIOPROTECTIVE PROPERTIES CONJUGATE DKV-11

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Abstract: This study determined the cardioprotective property of the conjugate (3,4-dihydroxyphenyl) -6- [1- (2′-bromo-4′, 5′-dimethoxyphenyl) -6,7-dimethoxy-3,4-dihydroisoquinoline-2 (1n) -yl] methyl-3,5,7-trihydroxychroman-4-он (DKV-11) under conditions of hypoxia and oxidative stress on the activity of contraction of the papillary muscles of the rat heart. The contractile activity of papillary muscle preparations was studied in vitro using SI-BAM21-LC (World Precision Instruments Inc. (WPI); USA) on a device that registers the force of muscle contraction using mechanography. When evaluating the cardioprotective properties of the DKV-11 conjugate in an in vitro model of hypoxia caused by the replacement of 95% O_2 and 5% CO_2 in an incubation medium with 95% N_2 and 5% O_2 and in the presence of H_2O_2 (100 μM) under conditions of hypoxia and oxidative stress. The study showed that the DKV-11 conjugate had an effective cardioprotective property based on a positive inotropic effect on the contractile activity of the papillary muscles of the rat heart.

Keywords: papillary muscle, positive inotrope, hypoxia, oxidative stress, conjugate.

Despite significant progress in the treatment of ischemic heart diseases today, this disease is in the leading position in the overall structure of death, and cardioprotection is one of the most urgent and priority areas of prevention and treatment of cardiovascular diseases. [1]. In the modern concept of prevention and treatment of these diseases in developed countries, the development of new

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approaches aimed at preventing damage to cardiomyocytes due to ischemia has a special place, which allows the creation of new pharmacological agents of highly effective cardioprotective agents. The main factor in the pathogenesis of these diseases is hypoxia, which develops in conditions of lack of oxygen, disrupting the coronary and cerebral blood circulation, which is accompanied by damage to the production of ATP and creatine phosphate, the main sources of energy in cardiomyocytes, as well as the transport of Na^+, K^+ and Ca^{2+} ions. and their transmembrane distribution is disturbed, which is accompanied by acidosis of the intracellular environment and accumulation of Ca^{2+} ions, which leads to energy damage and violation of contractile processes in the myocardium [2,3].

The purpose of the work is to study the effect of DKV-11 conjugate based on dihydroquercetin flavonoid with cardioprotective activity and 1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline alkaloid on the papillary muscle contraction activity of the rat heart under hypoxia conditions in vitro.

MATERIALS AND METHODS

The experiments were carried out on papillary muscle preparations (diameter 0.5-0.8 mm, length 1-3 mm) isolated from the right ventricle of the heart of white, purebred rats (200-250 gr.) and placed in a special experimental chamber. Preparations in the experimental chamber are constantly treated with Krebs solution of the following content (mM): NaCl-118; KCl-4.7; $CaCl_2$-2.5; $MgSO_4$-1.2; KH_2PO_4-1,1; glucose-5.5; $NaHCO_3$-25, pH-7.4 was perfused. Krebs solution is oxygenated with carbogen (O2 - 95%, SO2 - 5%) at a temperature of 35° C. The effect of F-18 alkaloid on the activity of myocardial contraction was carried out in the isometric mode in vitro in the mechanographic method of muscle contraction force recording device SI - BAM21 - LC (World Precision Instruments Inc. (WPI); SShA). In this device, the mechanical signal was received using the SI - piezoelectric sensor KG20

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SI - BAM21 - LCB device. The signal transmitted through the amplifier was transferred to the PK in digital format and recorded using the iWorx LabScribe2 special program, and was analyzed mathematically and statistically. The muscle preparation was stimulated with an ESL-2 stimulator and Pt-electrodes at a frequency of 0.1-3 Hz, with a duration of 10 ms, with a current strength 20% higher than the step level.

These studies are performed under normal physiological conditions and in vitro models of hypoxia and oxidative stress. Hypoxia and oxidative stress models are created by replacing 95% oxygen in the incubation medium with 95% nitrogen and adding hydrogen peroxide (N_2O_2). The results of the conducted research were analyzed based on the statistical program OriginPro 7.5 (OriginLab Corporation, USA).

RESULTS OBTAINED AND THEIR ANALYSIS

In recent years, molecular hybridization has been considered as a promising approach to create a new generation of cardioprotective agents, as a result of which it is possible to create new drugs that combine different pharmacological activities in one molecule. The advantage of this approach is that it provides an opportunity to obtain complex-acting drugs with improved pharmacokinetic properties due to the ability to simultaneously modulate various targets associated with defects in the pathogenesis of the disease. [4,5].

When we examined the dose-dependent effect of the DKV-11 conjugate on the contractile activity of the papillary muscle of the rat heart in experiments, it was found that this conjugate had a positive inotropic effect at all concentrations. Initially, DKV-11 conjugate had no significant effect on papillary muscle contraction from 1 μM to 5 μM, and a positive inotropic effect was absent from 5 μM. It was found that the DKV-11 conjugate had a maximum effect at a concentration of 35 μM and

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increased muscle contraction force by 77.4±4.4%, respectively, compared to the control (Figure 1). In this case, the half-maximum effective concentration (EC50) of the DKV-11 conjugate was -9.7±4.3 μM, respectively.

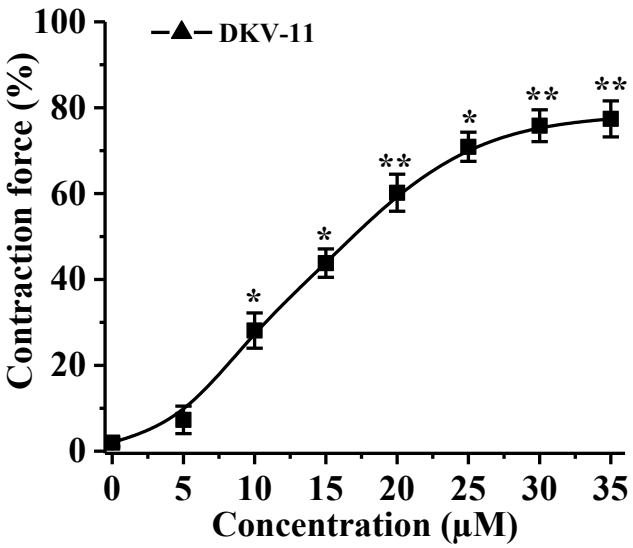

Figure 1. Dose-dependent effect of DKV-11 on papillary muscle contraction force. On the ordinate axis - muscle contraction strength is given in percent, on the abscissa axis - the concentration of DKV-11 (μM). In all cases (*p<0.05, **p<0.01; n=5). (The frequency of excitation of the drug is 1 Hz.)

To evaluate the potential/cardioprotective activity of DKV-11, an in vitro hypoxia model obtained by replacing oxygen with nitrogen in the perfusing Krebs solution was used. In the assessment of the effect of hypoxia and the potential cardioprotective activity of the compound, a maximal change in papillary muscle contractile activity was observed under conditions of replacing oxygen in a solution perfused with nitrogen for one hour.

Based on the experiments, it can be seen in Figure 2 that after perfusion with nitrogen for 60 minutes, the force of papillary muscle contraction was found to decrease to 26.6±3.1% compared to the control.

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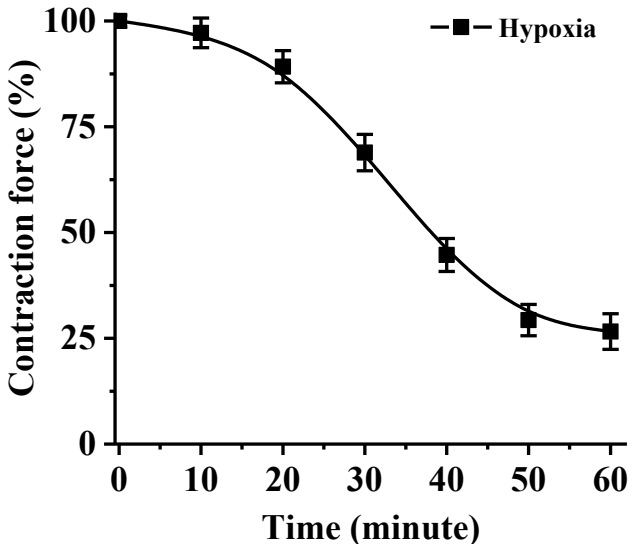

Figure-2. Effect of hypoxia on the contractile activity of the papillary muscle of the rat heart. On the ordinate axis - muscle contraction force, the control obtained under normal oxygenation of physiological solution is expressed as a percentage and taken as 100%. On the abscissa axis is the deoxygenation time of the solution perfused with nitrogen. The drug was stimulated with a frequency of 1 Hz. In all cases P <0.05, (n = 5).

Considering that the force of papillary muscle contraction is carried out with the participation of Ca^{2+} ions, the results of these experiments show that the decrease in muscle contraction force under hypoxia is accompanied by a decrease in $[Ca^{2+}]i$ ions. [6,7,8].

In control experiments, DKV-11 had a positive inotropic effect and increased the force of contraction of the papillary muscle. At the same time, this effect of DKV-11 dose-dependently increased the contraction force of the papillary muscle at a concentration of 35 μM by 177.4±4.4% compared to the control. When studying the effect of DKV-11 (35 μM) on papillary muscle contraction force under hypoxia conditions, it was found that it almost eliminated the impairment of papillary muscle

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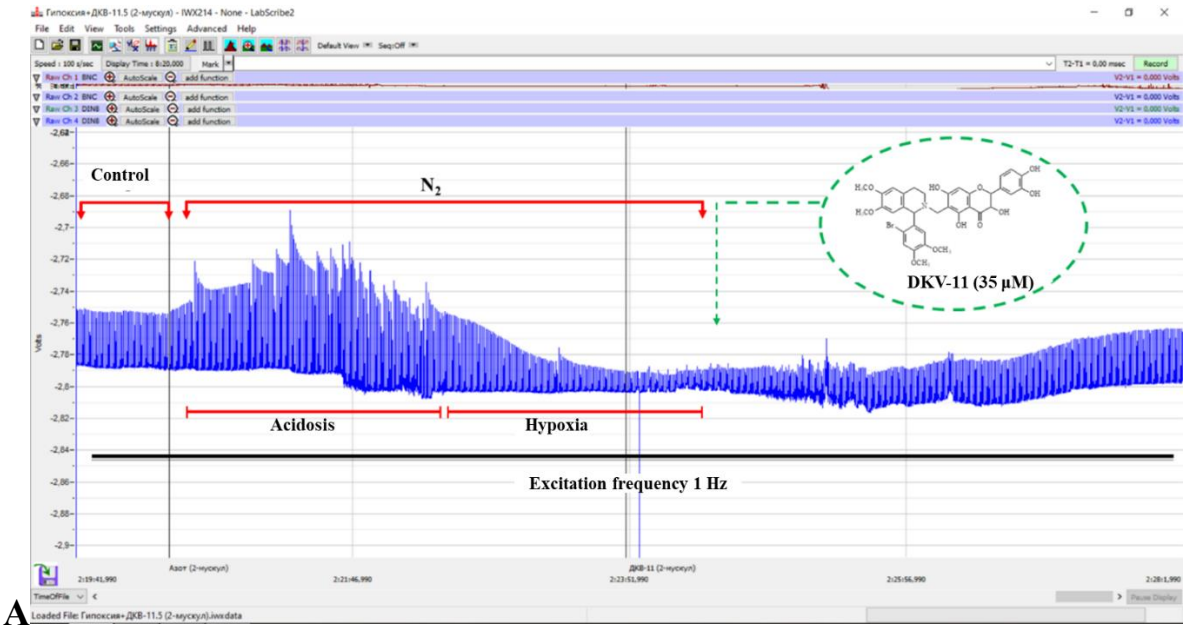
contraction activity caused by hypoxia and restored the muscle contraction force to 88.8±4.3% (3 A,B- picture).



A

Figure 3 A. Effect of DKV-11 on papillary muscle contractile activity of rat heart under hypoxic conditions (original text).

B

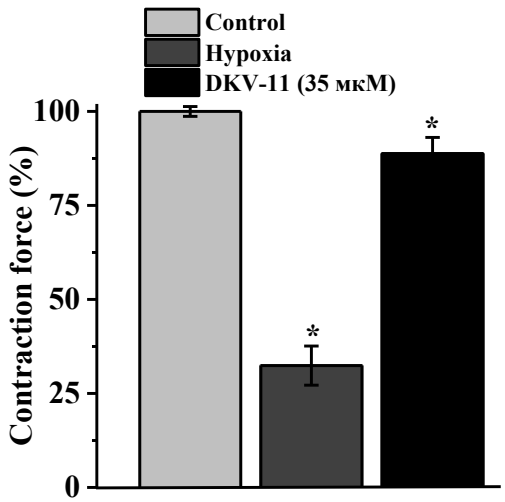


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Figure 3 B. Effect of DKV-11 on papillary muscle contractile activity of rat heart under hypoxic conditions. On the ordinate axis - the contraction force of the muscle is given in percent. *p<0.05 in all cases; n=8; drug excitation frequency 1 Hz.

It was observed that hypoxia did not occur when hypoxia was induced in the presence of almost DKV-11 (35 μM) in the incubation medium. The presence of DKV-11 in the medium reversed hypoxia-induced decrease in muscle contraction force. However, we found that DKV-11 prevented hypoxia-induced reduction in papillary muscle regeneration under the present conditions.

From the results of this experiment, it can be concluded that the DKV-11 conjugate effectively eliminates the disturbances in papillary muscle contraction under the conditions of experimental hypoxia induced by nitrogen.

In further experiments, the cardioprotective properties of DKV-11 under oxidative stress conditions (in the presence of 100 μM N2O2) were investigated to further clarify the cardioprotective properties based on the positive inotropic effect of DKV-11 on papillary muscle contraction activity (Figure 4).

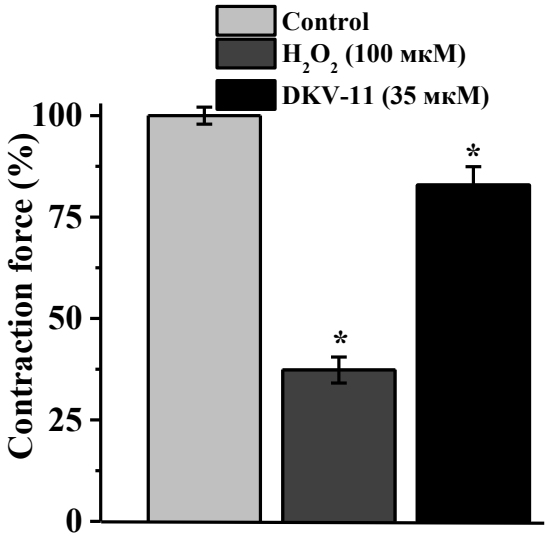

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Figure 4. Effect of DKV-11 on the contractile activity of rat heart papillary muscle under oxidative stress conditions. On the ordinate axis - the contraction force of the muscle is given in percent. In all cases *p<0.05 n=7; drug excitation frequency 1 Hz.

In preliminary control experiments, 100 μM H_2O_2 was found to reduce papillary muscle contraction force by 34.6±4.7%. Under these conditions, DKV-11 (35 μM) was observed to increase the force of papillary muscle contraction by 82.9±3.6%.

From the results of the conducted research, it can be concluded that the studied DKV-11 conjugate has an effective cardioprotective property based on its positive inotropic effect on the activity of papillary muscle contraction of the rat heart. This is further confirmed by the results of experiments conducted under conditions of in vitro hypoxia induced by aeration of Krebs physiological solution with 95% N_2 / 5% O_2 and the results of studies conducted under conditions of oxidative stress with N_2O_2.

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