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Tarasova A.P., Danilenko L.M., Sernov L.N. Effect of pharmacological preconditioning with incretinomimetics exenatide and vildagliptin on the survival of ischemic tissues. Research Result: Pharmacology and Clinical Pharmacology. 2017;3(4):132-150.

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EFFECT OF PHARMACOLOGICAL PRECONDITIONING WITH INCRETINOMIMETICS EXENATIDE AND VILDAGLIPTIN ON THE SURVIVAL OF ISCHEMIC TISSUES

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Abstract

Introduction: Currently, much attention is paid to the pleiotropic effects of entretenimiento.

Purposes: Study of the protective effect exenatide and valdiation with pharmacological correction of ischemic myocardial damage, damage of liver and skin graft during the experiment.

Methods: During the experimental study we used a comprehensive approach to the study of the antiischemic effects of entretenimento: doksorubitsinola model of cardiomyopathy, hypo/reperfusion of the isolated heart, ischemia/reperfusion of the liver and the modeling of the skin flap on the supply leg.

Results and discussion: Exenatide (10 mcg/kg/day) and vildagliptin (0.2 mg/kg/day) demonstrate a cardioprotective effect on doxorubicinol model of pathology that is reflected in the decline in the rate of diastolic dysfunction (S_{fTTI}), respectively, to 5.3±0.1 standard units. and 6.5±0.2 standart units in comparison with the control group 8.3±0.1 standart units in the model hypo/reperfusion of the isolated hearts of rats, exenatide (10^{-6} mol/l) and vildagliptin (10^{-4} mol/l), prevent the decrease of left ventricular pressure (LG). Exenatide (10 μg/kg) and vildagliptin (0.2 mg/kg) prevent necrotization of the skin flap 1.5 and 1.3 times in comparison with the control group. In the model of ischemia/reperfusion of the liver exenatide possess dose related hepatoprotective effect. All protective effects of entretenimiento leveled combined with a blocker of ATP-sensitive potassium channels glibenclamide (0.4 mg/kg).

Conclusion: During the study it was found that exenatide dose of 10 μg/kg/day and vildagliptin dose of 0.2 mg/kg, have a pronounced cardioprotective, hepatoprotective, and a pronounced cytoprotective effect on a model of isolated skin flap on the supply leg. ATP-dependent potassium channels are effector mechanism in the implementation of the protective effects of entretenimiento.

Keywords: entretenimiento, exenatide, vildagliptin, doksorubitsinola cardiomyopathy, isolated heart of rats, ischemia.

Introduction

New substances with cardiotropic effects are being identified among various classes of chemical and pharmacological groups [1, 2, 3, 4, 5, 6].Currently aspects of cardiovascular safety are a priority when choosing individual tactics of patients with type 2 diabetes mellitus (T2DM) [7, 8]. It is possible to assume the lack of increase of the risk of cardiovascular disease (CVD) in patients with T2DM when using drugs incretin series[9, 10, 11]. Furthermore, the results of experimental and clinical studies highlight the potential cardioprotective properties of these drugs [12, 13].

Accumulated results in recent experimental and clinical studies allow to speak about

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pleiotropic effects of entretenimiento [14]. The receptors of GLP-1 are detected in endothelia and cardiomyocytes, monocytes, macrophages, neurons, bone tissue, adipose tissue and other target organs [15, 16].

The great interest represents the study of cardioprotective and antiischemic effects of entretenimiento exenatide and vildagliptin. The exact mechanisms underlying their effects on different organs and tissues, are still not established [13, 15, 17, 18, 19]. The discussed effect is the one of ischemic preconditioning, where the implementation of effects can be done through opening of mitochondrial K-ATP channels, which can be a state trigger preconditioning [20]. The evidence of the activation of antiapoptotic pathways as one of the possible mechanisms of the cardioprotective effect of early ischemic phase of preconditioning are obtained. The most likely is the protective effect of peptide growth factors including insulin, insulin-like growth factor 1, transforming growth factor beta-1, cardiotrophin-1 and growth factors of fibroblasts, caused by the relatively reperfusion injury of the myocardium associated with apoptosis through inhibition of P42/P44 MAR-kinazy and the P13-channals/Akt-signaling [21, 22, 23, 24]. The pharmacological preconditioning with incrimination can also be realized via NO/cGMP-dependent mechanism which is also involved in cardioprotective effects of entretenimiento [25, 26].

It is anticipated that GLP-1 may also have a positive impact on oxidative stress and endogenous antioxidant defense mechanisms, through the increased expression of heme-oxygenase-1(HO-1) [27, 28], while having a positive impact in myocardial cardioprotection [29, 30].

Purposes: The study of the protective effect of pharmacological preconditioning with incrimination exenatide and valdiation when pharmacological correction of ischemic myocardial damage, the damage of liver and skin graft in the experiment.

Methods

The experiments were performed on male and female rats of Wistar line weighing 200-250 g . The experimental animals are obtained from the Laboratory animal nursery "Stolbovaya" of Governmental Institution The Scientific Center of Biomedical Technologies Russian Academy of Medical Sciences (Moscow region). The contents and their care were carried out according to the recommendations of State Standard – 53434-2009 "Principles of good laboratory practice" International guidelines "of the European Convention for the protection of vertebrate animals used for experimental and other scientific purposes" (The European Convention, 1986). All the experiments were approved by the local Ethics Committee (Protocol No. 12-2014 dated 21st January 2015).

Modeling of doxorubicinol cardiomyopathy

During the simulation of the doxorubicinol cardiomyopathy, all the rats were divided into 4 experimental groups of 10 animals. The first group (n=10) the control one, which was injected intraperitoneally with physiological solution. The second group (n=10) was injected intraperitoneally with doxorubicin (Teva) in a cumulative dose of 20 mg/kg, once. The third one (n=10) was injected doxorubicin and intraperitoneal vildagliptin ("Galvus", Novartis, Switzerland) at a dose of 0.2 mg/kg/day. The fourth group (n=10) was injected doxorubicin and exenatide subcutaneously once per day ("Beta", Eli Lilly and Company, USA) at a dose of 10 mg/kg/day. The doses were calculated considering the coefficient of interspecies transfer of doses of the human body on the body of the rat. Animals were taken out from experiment after 48 hours. Their hearts were removed under zolotilova anesthesia (30 mg/kg) and placed in the ice (2-4°C) solution of Krebs-Henseleit the following composition (mmol): NaCl 118.5; KCl – 4.7; MgSO4/7H2O – 1.2; KH2PO4 – 1.2; CaCl2 – 1.5; glucose, 11.1; NaHCO3 -25.0. The pH of the solution during the whole experiment was 7.4. The aorta of the heart was coulibalied and produced by retrograde perfusion of the heart method of Langendorff in the mode of flow perfusion for 20 min with a solution of Krebs-Henseleit, saturated with Carbogen (95 % O2 + 5% CO2) at 37°C and at a pressure of 100 mm Hg and speed perfusate 10 ml/min. The

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contractile function of the heart was recorded with the help of the inserted into the cavity of the left ventricle a latex balloon connected to a pressure sensor embedded in the device for physiological studies MP150 company "BiopacSystems, Inc" (California, USA). The balloon was filled with distilled water, the volume of which was sufficient to create end-diastolic pressure in the left ventricle at the level of 3-5 mm Hg. Using the original software program, AcqKnowledge company "BiopacSystems, Inc" (California, USA), all rats were checked for the indices of contractility: left ventricular pressure (LG, mm Hg), heart rate (HR, beats/min), the maximum rate of contraction (+dp/dtmax, mm Hg/sec), the maximum speed of myocardial relaxation (-dp/dtmax, mm Hg.St./sec). To create a high frequency (480 beats/min.) a connector (ground electrical stimulator) was attached to a to the metallic cannula, and a left atrial appendage was joined by a connector. After 20 minutes of perfusion with a solution with a high content of Ca^{2+}(5 mmol/l), the heart was subjected to electrical stimulation pulses using the STM device 200-1 of the company "BiopacSystems, Inc" (California, USA) for 15 seconds.

To assess the functionality of the myocardium, the diastolic dysfunction ratio or "diastole defect" (S_{tTTI}) calculated from the intraventricular pressure curve was used. The area under the curve was calculated by folding the trapezium areas, which is equal to the product of its height on the middle line. "diastole defect" (S_{tTTI}) expressed in the us [31].

Integrated assessment of myocardial damage in doxorubicinol cardiomyopathy in animals have identified the isoenzyme CPK (CPK-MB) and lactate dehydrogenase (LDH). The activity of lipid peroxidation (LPO) was evaluated by the content of malondialdehyde (MDA), diene conjugates (DC).

Hypo-reperfusion in isolated heart of rats

In epy experiments on perfused according to Langendorf isolated rats' hearts we simulated hypo – and reperfusion injury (hypoperfusion a 10 – fold decrease in perfusion with normal content of Ca2+ (2.5 mmol/l) [32]. It was judged about the damaging

effect by the dynamics of indices of contractility and reperfusion fibrilace.

Hepatotropic antiischemic activity

The study of hepatotropic antiischemic activity entretenimiento was carried out in anesthetized animals, performing median laparotomy on the white line of the abdomen. Ischemia was simulated for 15 minutes. After that, the contents of the abdomen were laid back, and the operative wound was sutured in layers. The animals for 3 days were administered exenatide (10 mcg/kg/day) and vildagliptin (0.2 mg/kg/day) control group with 0.9 % solution of sodium chloride intraperitoneally.

At the end of 3 days after the experiment the animals were euthanized with subsequent blood sampling from the heart for biochemical analysis and selection of the whole liver to conduct morphological analysis. To assess the liver function there were chosen biochemical markers of damage to hepatocytes of ALT and AST. To assess structural changes there were made histological sections of specimens of liver of the experimental rats with subsequent morphological assessment [33].

Modeling of the skin flap on the supply leg

The possibility of optimizing the survival of the tissues was investigated in a model of isolated skin flap on the supply leg. All animals were performed the modeling of the skin flap on the leg on the second day of the experiment. After anesthesia the animals were fixed in supine position. The hair on the abdomen was carefully cut out, the skin was treated with 70% solution of ethyl alcohol. Margins of 1 cm from the xiphoid process on the white line of the abdomen, made the skin flap 1cm – base, 4 cm long, (keeping the supply vessel) insulated in a plastic bag, the edges of the skin sutured with a continuous suture. The estimation of the area of the surviving tissue was performed planimetrically on the fifth day. Further we calculated the survival rate (ratio of the area of the surviving fabric to the original square flap ×100%) [34].

Results and Discussion
Dynamics of functional, biochemical and morphological indicators in the simulation

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doxorubicinol cardiomyopathy, hypo/reperfusion of the isolated heart, ischemia/reperfusion of the liver and the modeling of the skin flap on the supply leg

For the evaluation of cardioprotective actions of pharmacological agents, including the modeling of the pathology of cardiomyopathy by administration of doxorubicin intraperitoneally at a dose of 20 mg/kg, 48 hours later, the assessment of parameters of left ventricular contractility in conditions of high rate reductions 480 beats per minute for 15 seconds on the background of increasing concentrations of $Ca2+$ and 5 mmol in perfusate on the isolated heart of rats as an additional criterion of assessment of cardioprotective actions of drugs used ratio S_{tTTI} reflecting "defect diastole" area under the curve of the rise of end-diastolic pressure. While intact rats have S_{tTTI} is 1.4±0.1 standard units, and in rats with modeling of the pathology of 8.3±0.3 standard units (Fig 1.)
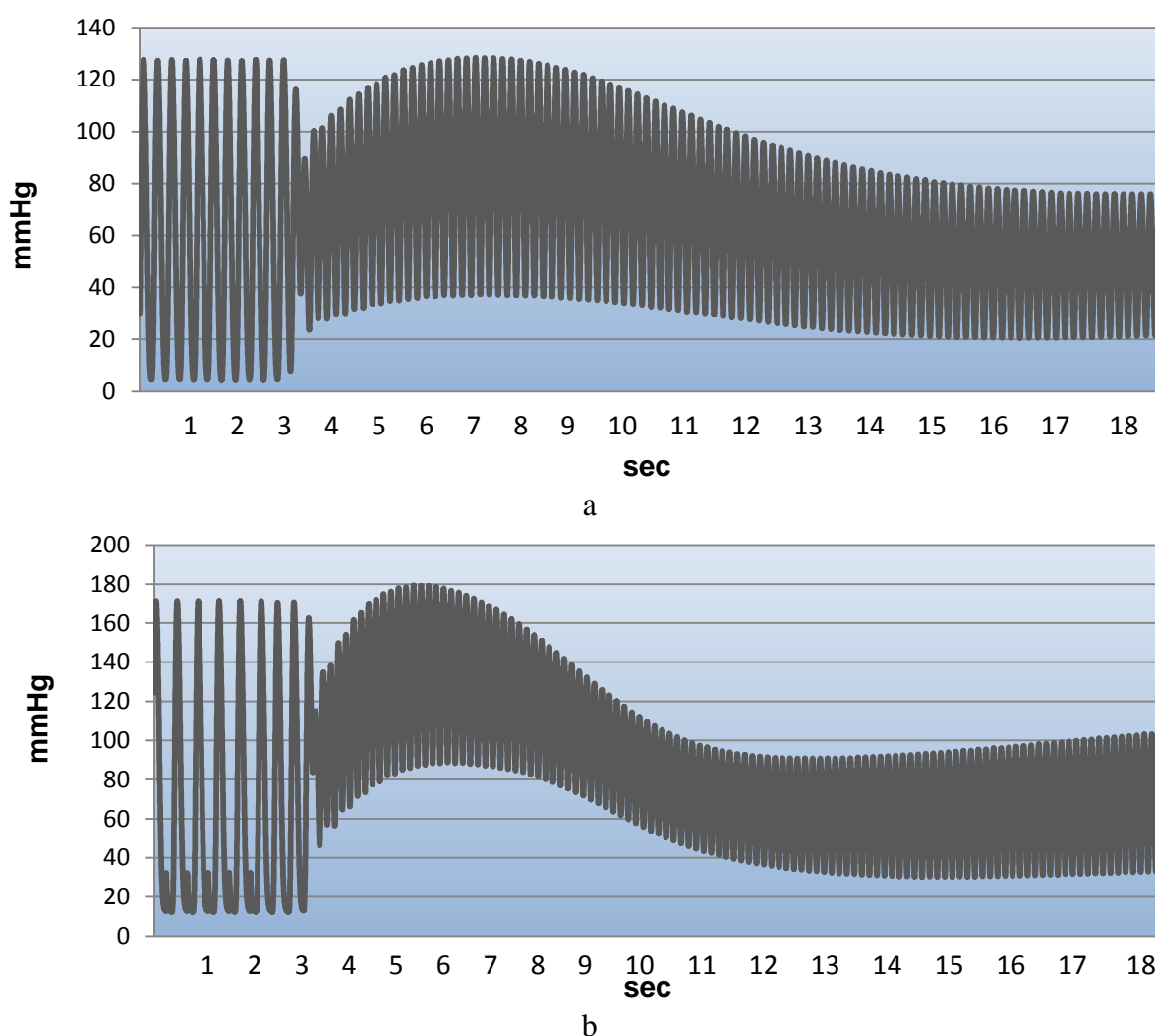

Fig. 1. Dynamics of pressure in the left ventricle (mm. Hg.) with the imposition of rapid heart rhythm contractions (480 BPM) for 15 seconds. The concentration of Ca^{2+} in perfusate 5 mmol/L. Intact group (a), doxorubicin (20 mg/kg) (b)

The fundamental difference in the area under the curve of the rise of end-diastolic pressure in the intact group and the control on the background of doxorubicin, naturally led to the necessity of introducing a factor S_{tTTI}, which is quite revealing and informative.

For a comprehensive evaluation of myocardial damage it was determined by the

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isoenzyme CPK (CPK-MB) and lactate dehydrogenase (LDH). The activity of lipid peroxidation (LPO) was evaluated by the content of malondialdehyde (MDA), diene conjugates (DC) (fig. 2).
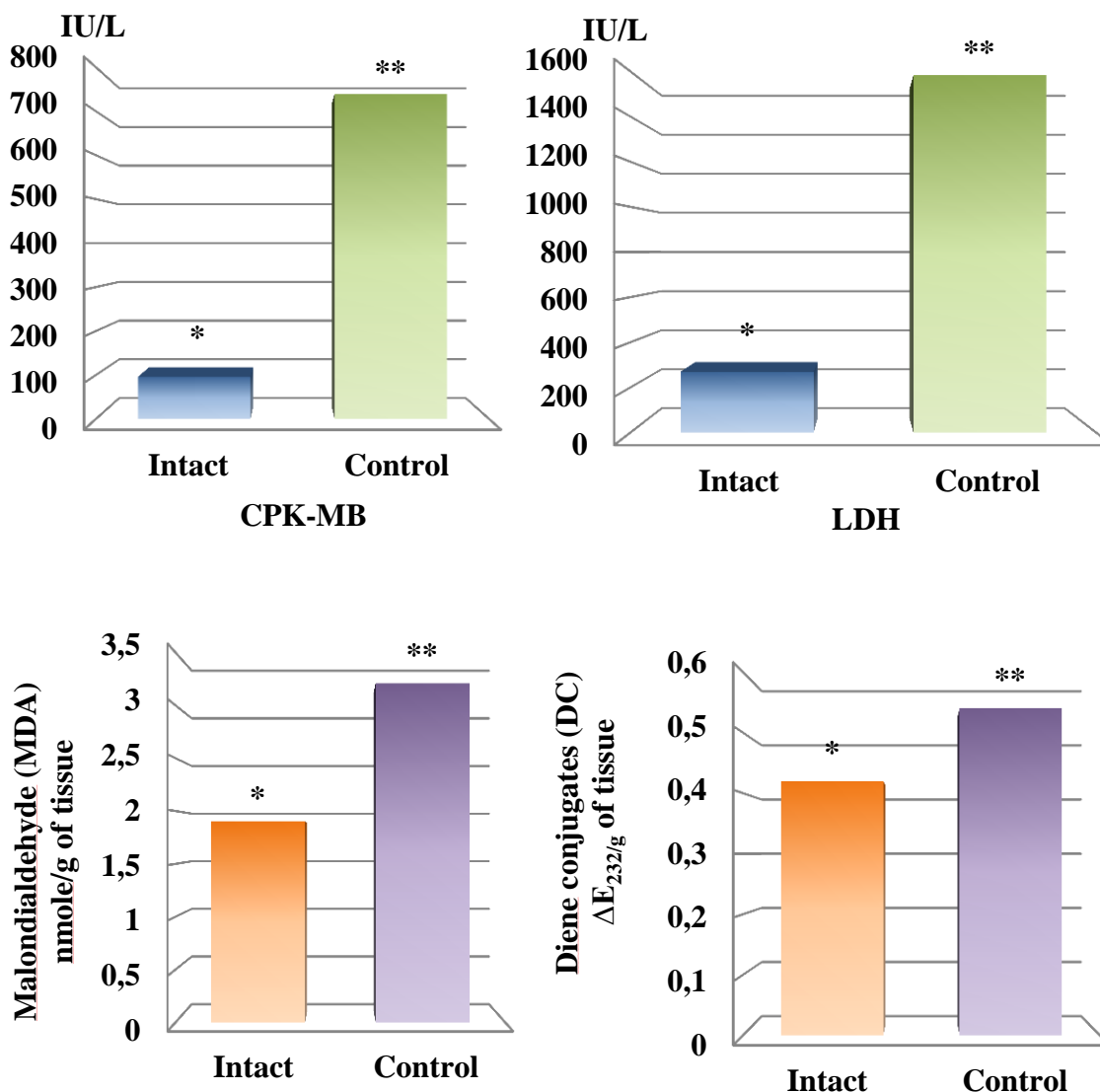

Fig. 2. The content of creatine phosphokinase CPK-MB, LDH, MDA, DK, in the model gypo/reperfusion in isolated hearts of rats.
Note: * p< 0.05 compared with control.** – p< 0.05 compared with intact animals

Investigation of the stability of the myocardium to ischemia/reperfusion damage were studied on the model of gypo/reperfusion in isolated heart of rats under register pressure in the left ventricle (LG). In studying the cardioprotective activity in the model Hypo- and reperfusion was discovered that a decrease in perfusion in 10 times (coronary hypoperfusion) occurs a marked drop in heart rate and contractility indices during the first 5min.By the 20th min of hypoperfusion HR, LR,+dP/dt$_{max}$, -dP/dt$_{max}$ were below the initial

values. Restore the original volume of perfusion (reperfusion) was accompanied by the development of reperfusion arrhythmias that in 3 cases out of 10 lead to fibrillation.

At the 5th min of reperfusion LG, +dP/dt$_{max}$, -dP/dt$_{max}$ remained below the initial level. A similar falling trend in the parameters of contractility was preserved and further to the 20th min of reperfusion, where LG, +dP/dtmax, -dP/dtmax were less than half the initial value (tab. 1).

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In the simulation laparotomy, there were statistically significant indicators of liver enzyme values. The imposition of a 15-minute ischemia with subsequent reperfusion of the liver statistically significantly raised levels of transaminases in average 5 times (tab. 2).

Table 1

Functional parameters of myocardium in gypo/reperfusion in isolated heart of rats (%of initial level) (M±m; n=10)

Indicators	The outcome	Hypoperfusion time		Reperfusion time	
		5 minutes	20 minutes	5 minutes	20 minutes
Heart rate, heartbeats per min	224.3±8.4	-64.6±3.2	-58.3±2.3	-16.6±10.3	-10.8±16.1
LG, mm Hg.	120.0±9.8	-65.8±7.5	-69.3±9.1	-19.8±8.1	-19.5±14.1
+ dp/dtmax, mm Hg.	2498±4.7	-76.7±2.5	-78.8±1.5	-19.8±14.1	-15.0±19.0
- dp/dtmax, mm Hg.	-1346±1.8	-71.6±2.0	-74.8±10.2	-36.6±10.4	-55.2±12.1

Note: LG – left ventricular pressure (mm. Hg.); +dp/dtmax maximal rate of reduction (mm Hg/sec); -dp/dtmax maximal rate of relaxation (mm Hg/h); HR – heart rate (beats/min).* – $p<0.05$ in comparison with the control group.

Table 2

Indicators of the level of transaminases in the simulation of Ieremii/reperfusion of the liver (U/l) (M±m; n=10)

Group of animals	ALT	AST
Intact	68.1±13.8**	102.8±8.9**
Lineameriloan	72.8±12.3**	110.2±10.3**
Control	216.9±16.8*[1]	189.1±13.2*[1]

Note: *–$p < 0.05$ compared with the group of intact animals; **– $p < 0.05$ in comparison with the false-operated group; 1– $p>0,05$ in comparison with the control group.

According to the study design, the assessment of the degree of survival of the skin flap on the leg was performed at 3, 7, 10 a day, then planimetrically after Avtandilov, measuring the area of surviving tissue. Further we calculated the survival rate (ratio of the area of the surviving fabric to the original square flap 100 %. The result revealed that the area of necrosis on the 10 day increases by 2.5 times (table. 3).

Table 3

Survival rates of the isolated skin flap on the supply leg at 3, 7, 10 days after its modeling. (M±m; n=10)

Drugs and their dosages	The area of necrosis KL, %		
	3 day	7 day	10 day
Saline (Control)	30.98±2.84	65.76±2.64	84.55±3.23

Note:* – $p<0,05$ in comparison with the control group

Thus, doksorubitsinola model of cardiomyopathy, Hypo/reperfusion in isolated hearts of rats, ischemia/reperfusion of the liver and the modeling of the skin flap on the supply leg are easily repeatable and informative models to assess of protective effects of drugs in ischemic tissues.

2. The study of cardioprotective, hepatoprotective, and cytoprotective effect in the model of isolated skin flap on the supply leg from exenatide and vildagliptin

Entretenimiento exenatide at doses (1 mg/kg/day and 10 mg/kg/day) and vildagliptin (0.02 and 0.2 mg/kg/day) did not affect the degree of decrease of contractility (table. 4).

However, dose-dependently we prevented the decrease in contractility during the tests

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with high-frequency stimulation. At the same time, S_{tTTI} for exenatide 10 µg/kg/day and vildagliptin 0.2 mg/kg/day was 5.3±0.1 and 6.5±0.2 us.ed. respectively (Fig. 3).

Table 4
The influence of entretenimiento exenatide and vildagliptin on the performance of the contractile function of the hearts of rats under doxorubicinol cardiomyopathy (M±m; n=10)

Groups of animals	LG	+dp/dt$_{max}$	-dp/dt$_{max}$	HR
IntactAnimals	87.3±9.2*	1423±162.2*	-1265.2±173.2*	248±32.1
Control Doxorubicin (20mg/kg)	64.5±11.2**	1025.7±154.3**	-1031.1±159.4**	247±29.4
Doxorubicin (20mg/kg)+ Exenatide (1 µg/kg/day.)	60.2±9.4**	1165,7±134.3**	-1109.9±119.4**	232±29.4
Doxorubicin(20mg/kg)+ Exenatide (10mcg/kg/day.)	76.8±7.4*	1302±169.2*	-1157.4±137.3*	231±26.9
Doxorubicin (20mg/kg) + Vildagliptin(0.02 mg/kg/day.)	59.1±10.7**	1107,7±15.,3**	-984.9±129.1**	227±29.4
Doxorubicin (20mg/kg)+ Vildagliptin (0.2 mg/kg/day.)	73.2±51*	1219±145.4*	-1108±169.3*	232±36.1

Note: the LG – left ventricular pressure (mm. Hg); +dp/dtmax maximal rate of reduction (mm Hg/sec); -dp/dtmax maximal rate of relaxation (mm Hg/h); HR – heart rate (beats/min). Doxorubicin was administered intraperitoneally, 48 hours before the experiment. Entretenimiento and vildagliptin exenatide were administered twice with an interval of 24 hours, subcutaneously and intraperitoneally, respectively, * * p<0.05 compared with the group of intact animals;* – p<0.05 in comparison with control group.
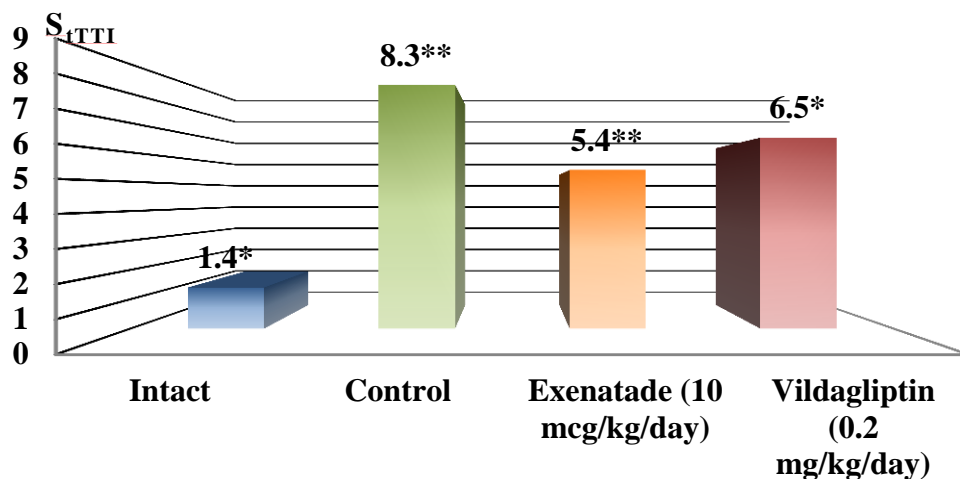

Fig. 3. The impact exenatide (10 mg/kg/day) and vildagliptin (0.2 mg/kg/day) for the coefficient of diastolic dysfunction (S_{tTTI}), with doxorubicinol cardiomyopathy.
Note: ** p<0.05 compared with the group of intact animals;
* – p<0.05 in comparison with control group

The values S_{tTTI} for exenatide at a dose of 1 mcg/kg/day and vildagliptin 0.02 mg/kg/day were not significantly different from the control group.

During the study of cardioprotective activity of incrimination on the model of Hypo/reperfusion it discovered that the addition of perfusiology solution exenatide at a dose of 10^{-6} mmol/l and vildagliptin 10^{-4} mmol/l, statistically znachimyh changes LG, +dP/dt$_{max}$, -dP/dt$_{max}$ and heart rate in the period of hypoperfusion to 20 min in comparison with the control was not detected. In the period of reperfusion, both entretenimiento prevented the fall in contractility and on the 5th and 20th min

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differed little from the original values, whereas in control, they fell by more than 50% (tab. 5).

In addition, unlike the control, the number of reperfusion arrhythmias decreased markedly.

Table 5

Cardioprotective action exenatide (10^{-6} mmol/l) and vildagliptin (10^{-4} mmol/l) with Hypo-reperfusion in isolated heart of rats (%of initial level)(M±m; n=10)

Indicators	Group of animals	Outcome	Hypoperfusion time		Reperfusion time	
			5 minutes	20 minutes	5 minutes	20 minutes
Heart rate, heartbeats per min	Control	224.3±8.4	-64.6±7.2	-58.3±8.3	-16.6±10.3	-10.8±14.1
	Exenatide	233.0±7.3	-3.2±6.4*	-53.5±5.3	+1.4±9.1*	+2.8±13.7 *
	Vildagliptin	221.3±7.8	-45.3±4.9 *	-54.6±7.2	-8.9±6.2*	-3.2±9.1 *
LG, mm Hg	Control	120.0±9.8	-65.8±7.5	-69.3±9.1	-19.8±8.1	-19.5±14.1
	Exenatide	116.8±7.1	-78.7±9.3	-62.6±8.8	-8.1±10.2*	-1.8±11.2*
	Vildagliptin	114.0±11.1	-67.0±8.7	-61.1±9.2	-6.4±9.4 *	-1.4±10.0*
+ dp/dt$_{max}$, mm Hg	Control	2498±4.7	-76.7±2.5	-78.8±6.5	-19.8±11.1	-15.0±12.0
	Exenatide	2309±7,5	-77.6±7.9	-75.7±10.1	-12.9±9.4*	+5.4±9.2*
	Vildagliptin	2325±6.9	-78.6±9.4	-76.8±5.5	-10.8±8.8*	+3.5±8.7*
- dp/dt$_{max}$, mm Hg	Control	1346±1.8	-71.6±5.0	-74.8±10.2	-36.6±10.4	-55.2±12.1
	Exenatide	1345±2.4	-69.1±9.7	-69.6±9.2*	-12.9±7.9*	+3.7±11.0*
	Vildagliptin	1265±5.7	-67.3±6.8	-70.5±7.4	-10.8±9.4*	+4.5±7.9*

Note: The LG – left ventricular pressure (mm. Hg.St); +dp/dtmax maximal rate of reduction (mm Hg./sec); -dp/dtmax maximal rate of relaxation (mm Hg./h); HR – heart rate (beats/min).* – p<0,05 in comparison with the control group.

The ability of exenatide 10 µg/kg/day and vildagliptin 0.2 mg/kg/day to prevent damage to cell membranes was estimated by the change in the activity of ck-MB and LDH. Exenatide and vildagliptin contributed to the decline in levels of creatine kinase-MB by 27% and 19% and LDH of 11.8% and 9.6% relative to the control group (figure 4).
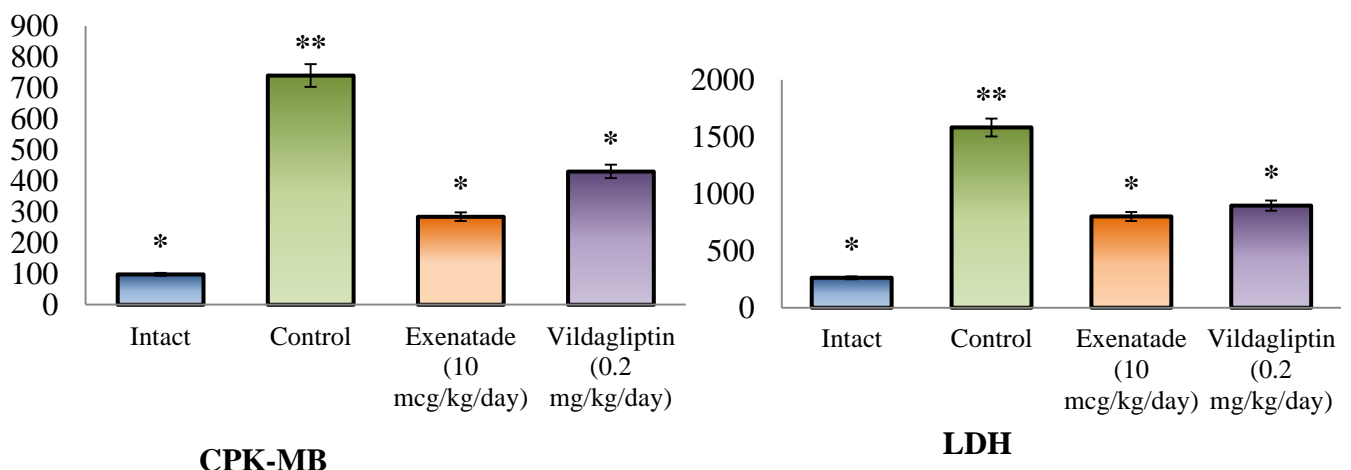

CPK-MB

LDH

Fig. 4. The content of creatine phosphokinase CPK-MB and LDH in groups with exenatide (10 mg/kg/day.) and vildagliptin (0.2 mg/kg/day).
Note: ** p<0.05 compared with the group of intact animals;
* – p<0.05 in comparison with control group

Similar changes were detected in the marker of the products of lipid peroxidation (figure 5).

The correction of the ischemic liver damage by exenatide (10 mg/kg/day) and vildagliptin (0.2 mg/kg) reduces the level of

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transaminases in 2 times, however, does not restore values to the original level (table 6).

Fig. 5. The contents of MDA and DC in homogenate in groups with exenatide (10 mg/kg/day.) and vildagliptin (0.2 mg/kg/day)
Note: ** p<0.05 compared with the group of intact animals;
* – p<0.05 in comparison with control group

Table 6

Indicators of the level of transaminases in modeling of schemia/reperfusion of the liver (U/l)
(M±m; n=10)

Group of animals	ALT	AST
Intact	102.89±8.9**	68.1±13.8**
Lineameriloan	110.2±10.3**	72.8±12.3**
Control	189.1±13.2*[1]	216.9±16.8*[1]
Exenatide (10 µg/kg/day)	130.2±10.9**	107.1±11.7**
Vildagliptin (0.2 mg/kg)	157.2±11.4**	145.8±13.4**

Note: *– p < 0.05 compared with the group of intact animals; **– p<0,05 in comparison with the false-operated group; [1] – p<0,05 in comparison with the control group.

The same trend is confirmed by the morphological picture of the liver (figure 6).

When modeling the skin flap on the supply leg, both studied entretenimiento contributed to the reliable correction to increase the area of surviving tissue in comparison with the control group at 3, 7 and 10 day. In the control group, the amount of necrosis amounted to 84.55±3.23%, in the group with exenatide and vildagliptin 63.18±2.42 and 76.08±2.53, respectively.
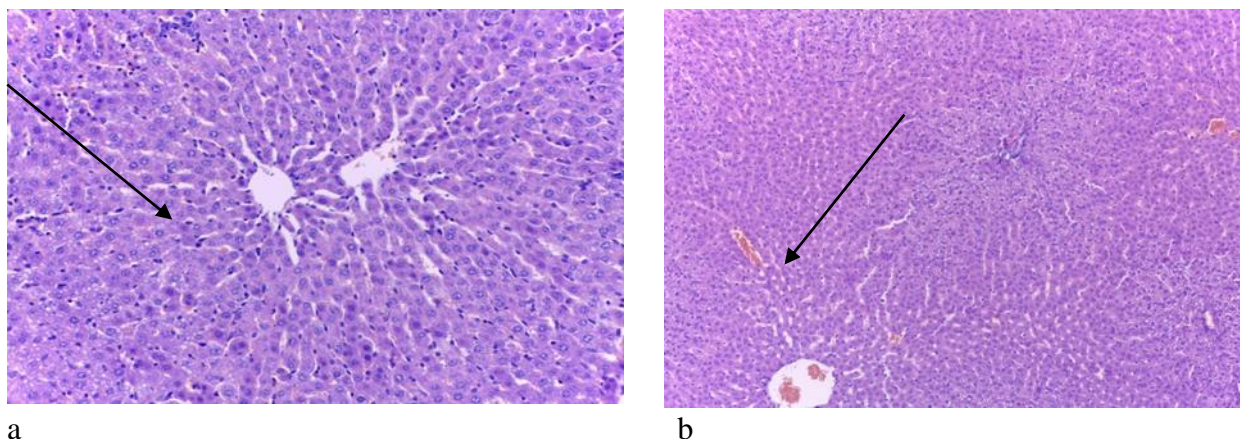
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a   b

Fig. 6. Morphological picture of the liver in a series of false-operated animals (a) and control group (b) micro photos. X400

Thus, on the totality of functional, biochemical and morphological indicators, entretenimiento exenatide (10 mg/kg/day) and vildagliptin (0.2 mg/kg) has a pronounced cardioprotective, hepatoprotective, and cytoprotective effects on the studied models of pathologies.

3. Defining of the role of ATP dependent potassium channels in the implementation of the protective effects of entretenimiento

The most likely effector link cytoprotective in the phenomenon of ischemic preconditioning are the ATP-dependent potassium channels.

The prior blockade of the ATP-sensitive potassium channels using intraperitoneal injection of glibenclamide dose of 5 mg/kg on the background modeling of the doxorubicinol cardiomyopathy, applications exenatide and vildagliptin led to the leveling effects of cardioprotection. The ratio of diastolic dysfunction S_{tTTI} in the group of animals treated with glibenclamide and exenatide and vildagliptin weren't significantly different from the control group and amounted to 7.5 ± 0.6 and 7.9 ± 0.7 standard unit (figure 7).
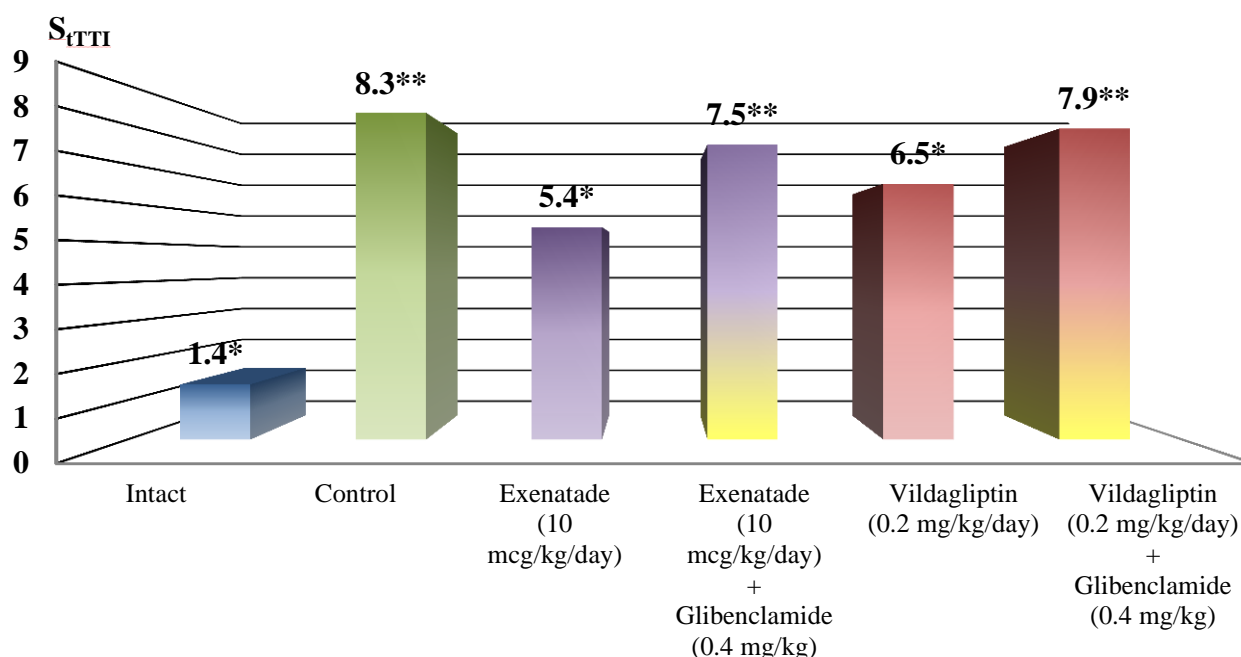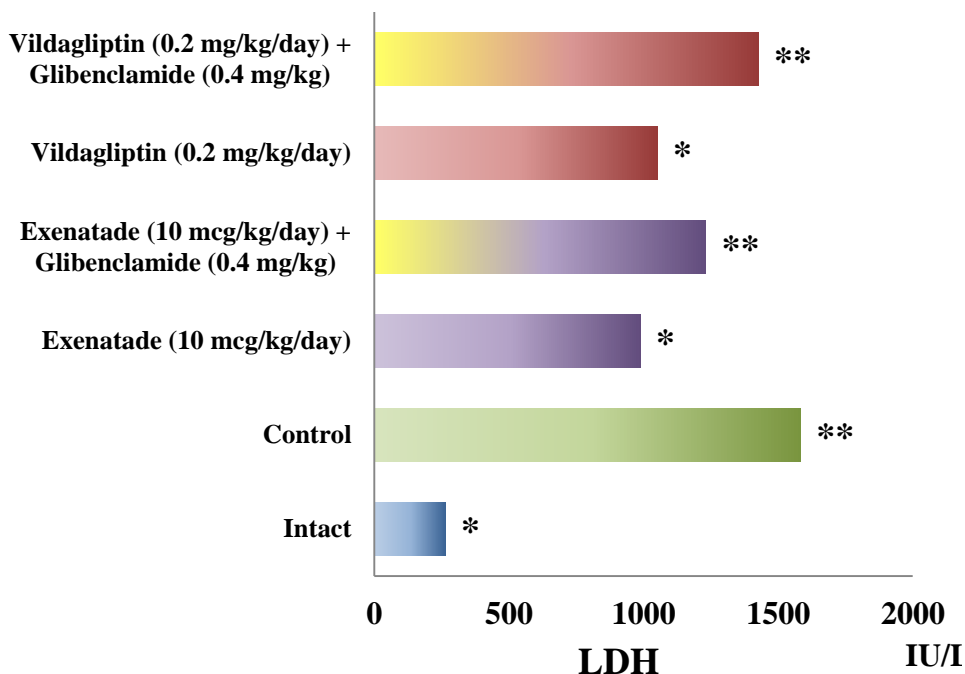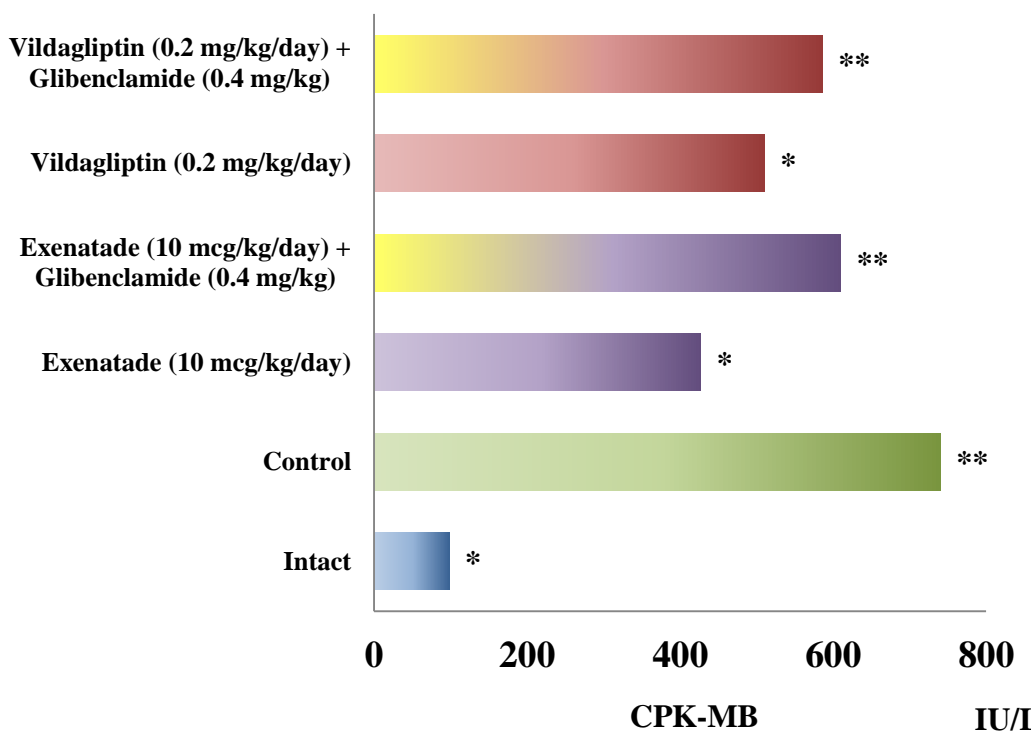

Fig. 7. The impact of the exenatide and vildagliptin on a factor of diastolic dysfunction (S_{tTTI}), with doxorubicinol cardiomyopathy.
Note: ** $p<0.05$ compared with the group of intact animals;
* – $p<0.05$ in comparison with control group

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Cardioprotective effects of incrimination were leveled with the introduction of the perfusate glibenclamide (10-6ммоль) fashion

Hypo/reperfusion in isolated hearts of rats. The level of biochemical markers and products of lipid peroxidation didn't reduce (figure 8).
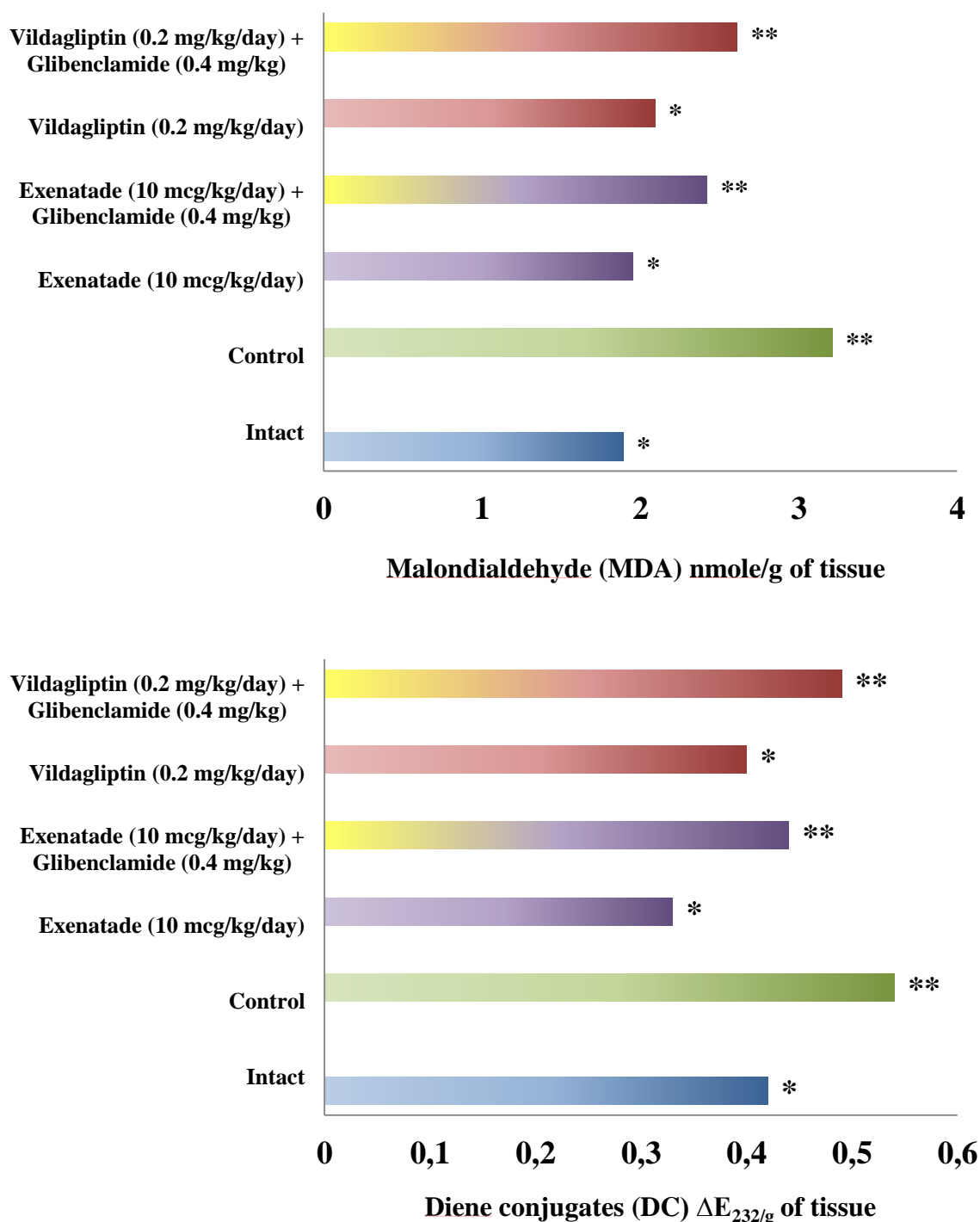
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Fig. 8. The content of CPK-MB, LDH, MDA, DK in the exenatide group (10 mg/kg/day.) and vildagliptin (0.2 mg/kg/day) in the model of Hypo/reperfusion in isolated hearts of rats.
Note: ** $p < 0.05$ compared with the group of intact animals;
* – $p < 0.05$ in comparison with control group

Entretenimento didn't show the pronounced hepatoprotective actions in the pre-blockade of ATP-sensitive potassium channels. The values of ALT and AST is comparable to the control group. That shows the lack of effect on the background of administration of glibenclamide (5 mg/kg) (table 7).

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Table 7

Protective action of exenatide and vildagliptin on transminase on the background of glibenclamide during ischemia/reperfusion of the liver (U/l). (M±m; n=10)

Group of animals	ALT	AST
Intact	68.1±13.8**	102.89±8.9**
Lineameriloan	72.8±12.3**	110.2±10.3**
Control	216.9±16.8*[1]	189.1±13.2*[1]
Exenatide 10 µg/kg/day	130.2±10.9**	127.1±11.7**
Exenatide 10мкг/kg/day +Glibenclamide 0.4 mg/kg	211.3±15.1**	175.6±13.2**
Vildagliptin 0.2 mg/kg	157.2±11.4**	145.8±13.4**
Vildagliptin 0.2 mg/kg+ Glibenclamide 0.4 mg/kg	202.90±16.9	169.4±8.1

Note: *–$p < 0.05$ compared with the group of intact animals; **– $p<0.05$ in comparison with the false-operated group; [1] – $p<0.05$ in comparison with the control group.

The prior blockade of ATP-sensitive potassium channels, completely negate the protective effect of entretenimiento when modeling of a skin graft on feeding pedicle in rats.

Table 8

Protective action of exenatide and vildagliptin on the background of glibenclamide survival of skin graft (%). (M±m; n=10)

Drugs and their dosages	The area of necrosis KL, %		
	3 day	7 day	10 day
Saline (control)	30.98±2.84	65.76±2.64	84.55±3.23
Exenatide (10 µg/kg/day)	24.37±3.12*	44.13±3.15*	63.18±2.42*
Exenatide (10мкг/kg/day) + Glibenclamide (0.4 mg/kg)	29.18±2.04	59.16±2.53	81.35±3.20
Vildagliptin (0.2 mg/kg)	26.10±2.83*	52.19±3.00*	76.08±2.53*
Vildagliptin (0.2 mg/kg) + Glibenclamide (0.4 mg/kg)	33.22±2.12	60.71±2.59	83.51±3.13

Note: *- $p<0.05$ in comparison with the control group

Nowadays, there is a large amount of data on the impact of GLP-1 and DPP on the cardiovascular system and various organs and tissues, the mechanisms of these effects differ from those mediated by the decrease of glycemia. The receptors of GLP-1 are widely represented in the body and, in addition to gastrointestinal tract, nervous system, lungs, kidneys, lymphocytes were found also in vascular smooth muscle cells, cardiomyocytes, endocardium and endothelial cells, which became the basis for the study of its cardiovascular effects [35, 36]. The receptors of GLP-1 (along with receptors for glucagon, secretin, calcitonin, somatoliberin, parathyroid hormone, vasointestinal peptide) belong to the class of the family of receptors associated with G-proteins (GCPR) [37]. In terms of the damage of ischemia—reperfusion cytoprotection is mainly due to the anti-apoptotic effect. GLP-1 binding to the receptor, suppresses apoptosis of β-cells and

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cardiomyocytes, by activating the formation of camp and fashionsitas-3-kinase (PI3-K) [38].

The activation of the RISK kinases (Reperfusion InjurySalvage Kinase), which includes PI3K and extracellular signal-regulated kinase (ERK 1/2). GLP-1 activates the serine-treoninove kinase (Akt). Favorable cardiotropic action of Akt is due to its ability to inhibit the processes of cell death of cardiomyocytes and to improve the survival rate of myocardial cells subjected to ischemia [39]. GLP-1 activates antioxidant gene hemeoxygenase-1 (HO-1). This enzyme prevents the heme catalyzed formation of highly reactive hydroxyl radicals from hydrogen peroxide. Activation of heme-oxygenase-1 is associated with increased catabolism of heme to bile pigments, which are potential endogenous antioxidants. In addition, the induction of heme-oxygenase-1 is accompanied by increased activity of ferritin, which has antiapoptotic effect. The increase in expression of heme-oxygenase-1 in conditions of oxidative stress may play an adaptive role in response to oxidative damage and reduce the loss of cardiomyocytes. In experimental studies it is shown that the modeling of the doxorubicin cardiomyopathy in transgenic mice and animals with excessive expression of HO-1 and cardiac-specific overexpression of HO-1 prevents doxorubicin-mediated damage to the sarcoplasmic reticulum and mitochondria in automagically the vacuoles [28]. Overexpression of HO-1 contributes to mitochondrial biogenesis by increasing protein expression of nuclear respiratory factor (NRF1), coactivator (PGC1α) and mitochondrial transcription factor (TFAM), which is inhibited in transgenic animals with doxorubicinol cardiomiopatia [40, 41]. Concurrently, overexpression of HO-1 inhibits the amplification of mitochondrial mediator of fission (Fis1) and leads to increased expression of mediators of synthesis of Mfn1 and Mfn2. It also prevents mutations in key genes of mitochondrial PINK1 and PARKIN and ensures their normal operation. This proves that the BUT-1 plays an important role in protecting heart from oxidative damage affecting the mitochondria . HO-1 is a protective antioxidant enzyme that acts through the induction of gene expression of nuclear transcription factor Nrf2, resulting in activation of Akt [42, 43].

Also, it is assumed that the positive effects of GLP-1 on myocardium may be due to activation of other signaling pathways (GSK3β, a family of proteins Bcl-2), and also due to the favorable effects of PPARs-β and -δ [43]. Cardioprotective effect of GLP-1 can be carried out through receptor-independent mechanisms. It is assumed that previously considered biologically inactive primary metabolite GLP-1 produced after interaction with DPP-4 and having a very low affinity to the receptor GLP-1 also plays a cytoprotective role by inhibiting the processes of cell death in cardiomyocytes in conditions of damage of ischemia (reperfusion through PI3 and ERK 1/2-dependent). The exact mechanisms of the effect of GLP-1 in ischemic injury remain unclear. One of them may be a direct stimulation of the receptors of GLP-1 on vascular smooth muscle cells that can be due to endothelium-dependent vasodilation (due to NO-dependent and NO-independent mechanisms) signaling pathways [44, 45].

Finally, the implementation of the protective effect of entretenimiento suggests mechanisms by type of ischemic preconditioning. End-effector link which can be considered as a mitochondrial ATP are the dependent potassium channels, whose activation leads directly to the increased resistance of the myocardium to ischemia. In addition, the experimental work of the last years showed that the cardioprotective effect of preconditioning can be completely (!) eliminated with the introduction of the RISK inhibitors of kinases (specifically ERK1/2 and PI3K), carried out during the initial period of reperfusion after the prolonged ischemia [46, 47, 48].

Hypothetical model of the mechanism of action of entretenimiento is presented in figure 9.
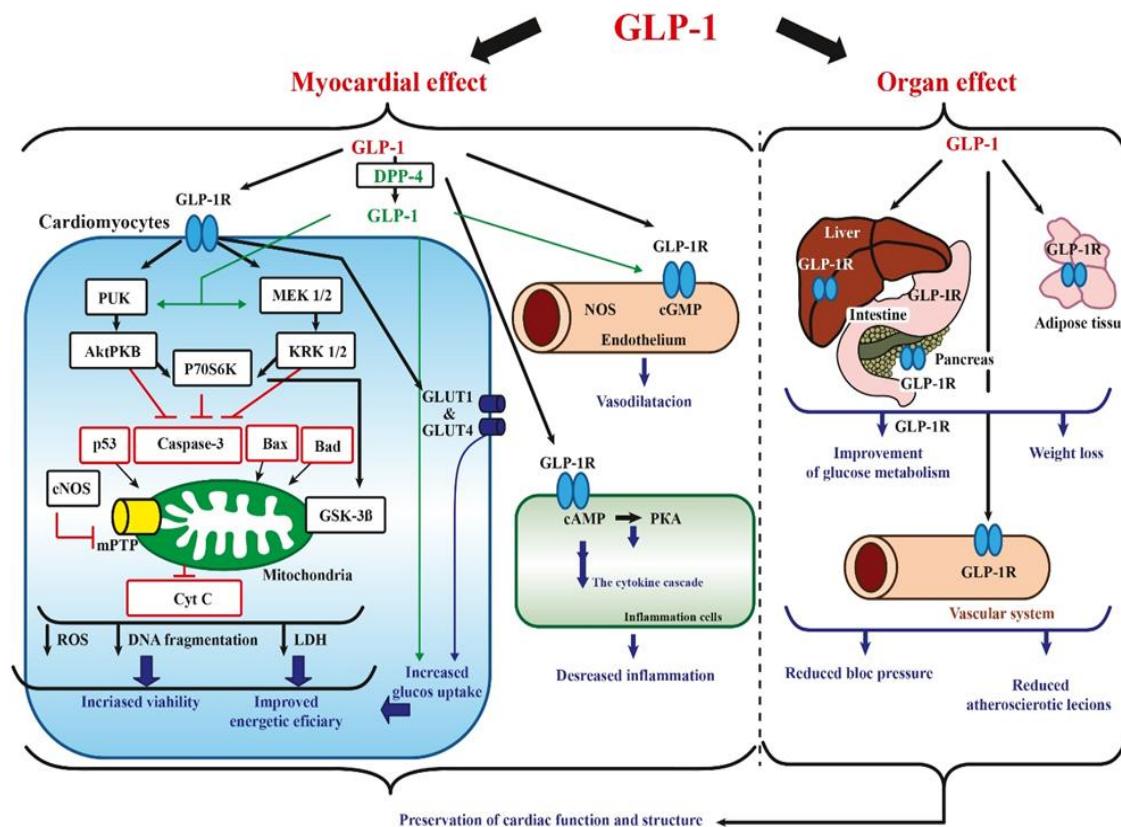
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Fig. 9. Schematic representation of the proposed pathways by which GLP-1 may exert its cardiovascular actions. The combination of GLP-1 effects on the myocardium (i.e. apoptosis and necrosis prevention in cardiomyocytes through the activation of the RISK pathway, increased glucose metabolism, vasodilatory and anti-inflammatory actions) with GLP-1 metabolic and vascular effects at the systemic level contributes to cardiac survival and function improvement

Note: cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; Cyt c, cytochrome c; DPP-4, dipeptidyl peptidase-4; ERK, extracellular signal-regulated kinase; GLUT, glucose transporter; GSK, glycogen synthase kinase; LDH, lactate dehydrogenase; MEK1/2, MAP kinase kinase; MPTP, mitochondrial permeability transition pore; NOS, nitric oxide synthase; PI3K, phosphatidylinositol 3-kinase; PKA, protein kinase A; PKB, protein kinase B; ROS, reactive oxygen species

However, the effects on the receptors GLP-1 and inhibition of DPP-4 require the further study.

Conclusion

Thus, in the course of the study it was revealed that doksorubitsinola cardiomyopathy (20 mg/kg, intraperitoneally for 48 hours) leads to the development of «the defect of diastole» increasing the area under the curve of left ventricular pressure 8 times. gypo/reperfusion (10:1, 20 min) in isolated hearts of rats leads to a decrease in LG by 2 times. Ischemia /reperfusion of the liver (15 min) leads to an increase in transaminases for 5 times (ALT and AST) and the characteristic dynamics of morphological patterns. The survival rate of skin flap on the leg are, respectively, 50, 60 and 70%. The proposed methods allow to provide a comprehensive evaluation of effects of pharmacological agents on the survival of ischemic tissues. Exenatide (10 µg/kg) and vildagliptin (0.2 mg/kg) exert a cardioprotective effect in the models of doxorubicinol cardiomyopathy, expressed in a

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reduction factor of diastolic dysfunction S_{tTTI} to values of 5.3±0.1 and 6.5±0.2 standard units respectively. In the model of gypo/reperfusion in isolated hearts of rats, exenatide (10^{-6} mol/l) and vildagliptin (10^{-4} mol/l) have a cardioprotective effect. Exenatide (10^{-6} mol/l) shows the most pronounced effect. Exenatide (10 µg/kg) and vildagliptin (0.2 mg/kg) prevent the necrotization of the skin flap in 1.7 and 1.5 times in comparison with the control group. In the model of ischemia/reperfusion of the liver exenatide (10 µg/kg) and vildagliptin (0.2 mg/kg) possess the dose related hepatoprotective effect, resulting the prevention of the increase of ALT and AST, and the morphological picture of the liver changes in the same way. All the protective effects of the exenatide (10 µg/kg) and vildagliptin (0.2 mg/kg) were neutralized in a joint application with a blocker of ATP-sensitive potassium glibenclamide channels (0.4 mg/kg). Consequently, ATP-dependent potassium channels may be the effector mechanism in the implementation of the protective effects of entretenimiento. NO acts as a trigger of ischemic preconditioning.

Conflicts of Interest
The authors have no conflict of interest to declare.

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