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EVALUATION OF CARDIOPROTECTIVE EFFECTS OF THE INCRITIN MIMETICS EXENATIDE AND VILDAGLIPTIN IN THE EXPERIMENT

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Abstract

Introduction: The results of experimental and clinical trials make it clear that incretin mimetics possess pleiotropic effects and demonstrate the value in terms of assessment of their potential opportunities as cardioprotectors.

Goals: To study the cardioprotective effects of exenatide and vildagliptin on the model of doxorubicin-induced cardiomyopathy.

Methods: The experiments on the Langendorf isolated rat heart were dedicated to the study of cardioprotactive activity of exenatide (10 mcg/kg/day) («Byetta®», Eli Lilly and Company, USA**)** and vildagliptin (0.2 mg/kg/day) («Galvus®», Novartis, Switzerland), on the contractile function of the isolated heart wich was previously perfused with doxorubicin (20 mg/kg, intraperitoneally before 48 hours). The evaluation of cardioprotactive activity was based on the findings of the functional trial with high-frequency stimulation (480 bmp) in hypercalcium (5 mmol) perfusion.

The complex evaluation of the myocardial damage in the flowing perfusate from isolated hearts included the assessment of creatine phosphokinase isoenzyme (CPK-MB) and lactic dehydrogenase (LDH). The activity of lipid peroxidation (LPO) was evaluated by measuring the content of malondialdehyde (MDA) and diethenoid conjugant (DC).

Results: Exenatide (10 mcg/kg/day) and vildagliptin (0.2 mg/kg/day) demonstrate a cardioprotactive effect on the model of doxorubicin-induced pathology, resulting in a decrease of diastolic dysfunction to 5.3±0.1 units and 6.5±0.2 units respectively, compared to control 8.3±0.1 units.

The cardioprotactive effect was confirmed by 45% and 30% decrease in the levels of CPK-MB marker damage, and by 36% and 24% decrease in LDH levels respectively in exenatide and vildagliptin series, compared to control. The cardioprotactive effect was also confirmed by prevention of accumulation of lipid peroxidation products of MDA and DC in the ventricular myocardium.

Conclusion: Exenatide (10 mcg/kg/day) and vildagliptin (0.2 mg/kg/day) decrease diastolic disfunction, resulting in the recovery of the contractile function of the heart, reduction of the "diastole defect" (S_{tTTI}), and the decrease in irreversible damages of cardiomyocytes.

Key words: incritinomimetics; exenatide; vildagliptin; doxorubicin-induced cardiomyopathy; isolated rat heart.

Introduction.

New substances with cardiotropic effects are being identified among various classes of chemical and pharmacological groups [1, 2, 3, 4, 5, 6, 7, 8]. Undoubted interest is represented by incretin mimetics , as a fairly new group of hypoglycemic agents with pleiotropic effects, in particular, cardioprotective [9, 10, 11, 12]. The exact mechanisms underlying the effect of GLP-1 on the cardiac muscle have not yet been established [13, 14, 15]. It is suggested that GLP-1 can positively influence the apoptosis of cardiomyocytes, oxidative stress, and endogenous antioxidant defense mechanisms, having a beneficial effect on cardioprotection of the myocardium [16, 17, 18, 19].

The formation of free radicals leads to an increase in oxidative stress, the triggering of apoptosis-mediated through iron ions calcium, NO-oxidase, glutathione peroxidase, neuregulin-1, protein kinase B, growth factors, cytokines and their

receptors, which may be a direct cause of doxorubicin-induced cardiomyopathy. The theory of oxidative stress in the development of doxorubicin-induced cardiopathy is the most popular, and often serves as an experimental model for studying the causes of apoptotic cell death and the selection of means for cardioprotection [20, 21].

Goals: To study the cardioprotective effects of exenatide and vildagliptin on the model of doxorubicin-induced cardiomyopathy.

Methods.

The experiments were carried out on 40 mature Wistar rats of both sexes weighing 220 ± 20 g. All animal manipulations were carried out in compliance with the "European Convention for the Protection of Vertebrates used for Experiment or Other Scientific Purposes" [Derective 2010/63/ EU]. All experiments were approved by the local Ethics Committee (Minutes No. 12-2016 of November 21, 2016).

All rats were divided into 4 experimental groups of 10 animals. The first group (n = 10), control, was intraperitoneally injected a saline solution. The second group (n = 10) was intraperitoneally injected with doxorubicin (Teva) at a cumulative dose of 20 mg/kg, once, the third (n = 10) – doxorubicin and intraperitoneal vildagliptin ("Galvus®", Novartis, Switzerland) at a dose of 0.2 mg/kg/day. The fourth (n = 10) – doxorubicin and exenatide ("Byetta®", Eli Lilly and Company, USA) subcutaneously once a day at a dosage of 10 mcg/kg/day. The doses of the drugs were calculated taking into account the coefficient of interspecific transfer of doses from the human body to the body of a rat.

The animals were withdrawn from the experiment after 48 hours. The hearts were removed from the animals under zolestal anesthesia (30 mg/kg) and placed in an icy (2-4°C) Krebs-Henselite solution of the following composition (mmol): NaCl – 118.5; KCl – 4.7; MgSO4/7H2O – 1.2; KH_2PO_4 – 1.2; $CaCl_2$ – 1.5; Glucose – 11.1; $NaHCO_3$ – 25.0. The pH level of the solution throughout the experiment was 7.4. After the termination of spontaneous contractions, the aorta was isolated and the connective tissue was separated. The aorta was then cannulated and retrograde perfusion of the heart was performed using the Langendorff method in a flow perfusion mode for 20 min with the Krebs-Henselite solution, saturated with carbogen (95% O_2 + 5% CO_2) at 37° C and 100 mmHg pressure and perfusate speed 10 ml/min.

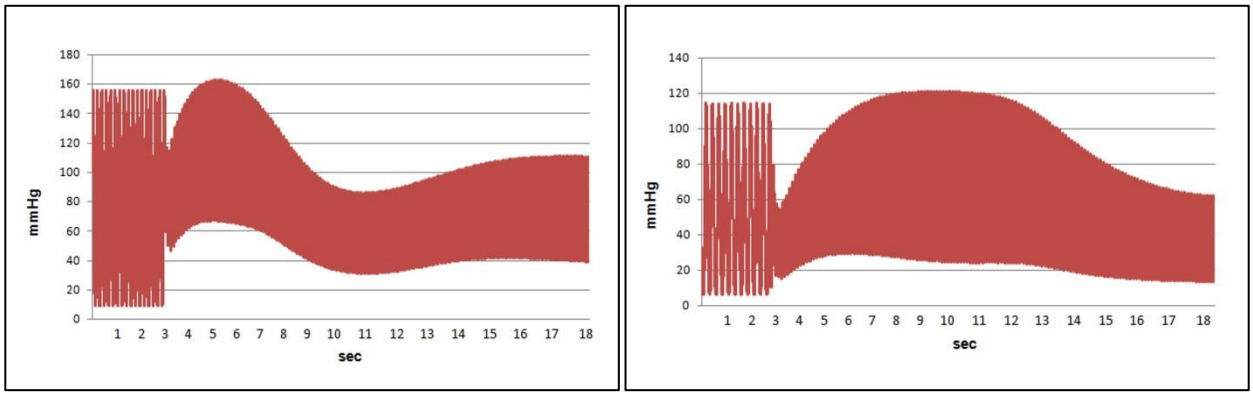
The cardiac contractility was recorded with a latex balloon inserted into the left ventricle cavity and connected to a pressure sensor built into the device for physiological studies of the MP150 of BiopacSystems, Inc. (California, USA). The can was filled with distilled water, the volume of which was sufficient to create a diastolic pressure in the left ventricle at a level of 3-5 mm Hg. With the help of the original AcqKnowledge application of the company "BiopacSystems, Inc." (California, USA), the contractility indices in the rats were recorded: left ventricular pressure (LVP, mmHg), heart rate (HR, bpm). The maximum rate of contraction (+dp/dt_{max}, mmHg/sec), the maximum relaxation rate of the myocardium (-dp/dt_{max}, mmHg/sec). To create a high frequency (480 bpm) a connector-ground of an electric stimulator was attached to the metallized cannula, and a connector-plus was attached to the eye of the left atrium. After 20 minutes of perfusion with a high Ca^{2+} (5 mmol / L) solution, the heart was stimulated with electrical pulses using the STM 200-1 device from 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. The "diastole defect" (S_{tTTI}) was expressed in units. The cardioprotective effects of the drugs vildagliptin and exenatide were judged by their effect on the S_{tTTI} index [22]. The damage markers and the level of peroxidation were evaluated by conventional methods [23, 24].

The reliability of changes in absolute parameters was determined by the difference method of variational statistics with finding the mean values of the shifts, the mean of the arithmetic mean, and the probability of possible error (p) from Student's tables. Differences between the values of the indices were considered statistically significant at $p < 0.005$.

Results.

Doxorubic myocardiopathy was characterized by a decrease in myocardial contractility (Table 1). Conducting a functional test with high-frequency stimulation revealed the development of the "diastole defect" (Fig. 1a), and S_{tTTI} increased to 8.3 ± 0.3 units in comparison with intact animals – 1.4 ± 0.1 units, in other words, it increased 8 times.



a b

Fig. 1. Exercise tolerance test under submaximal electrical stimulation of a rat heart isolated by Langendorf. Ca^{2+} concentration in perfusate – 5 mmol/L. Intact group.Pressure profile in the left ventricle (mmHg) at imposing qickened heartbeat (480 bpm) within 15 sec. Ca^{2+} concentration in perfusate – 5 mmol/L. Doxorubicin (20 mg/kg) given at a single dose within 48 hours (**a**). Intact group (**b**)

The incretin mimetics of exenatide in doses (1.0 mg/kg/day and 10 mcg/kg/day) and vildagliptin (0.02 and 0.2 mg/kg/day) did not affect the degree of decrease in contractility rates (as reflected in the Table) and dose-dependently prevented a decrease in contractility when carrying out the test with high-frequency stimulation. Thereat, S_{tTTI} for exenatide 10 mg/kg/day and vildagliptin 0.2 mg/kg/day were 5.3 ± 0, 16.5 ± 0.2 units respectively.

Table 1

Effects of incretin mimetics exenatide and vildagliptin on indices of contractile function /of the heart of rats with doxorudicine cardiomyopathy (M ± m; n = 10).

Groups of animals	LVP	$+dp/dt_{max}$	$-dp/dt_{max}$	HR
Intact animals	87.3±9.2*	1423±162.2*	-1265.2±173.2*	248±32.1
Doxorubicin control	64.5±11.2**	1025.7±154.3**	-1031.1±159.4**	247±29.4
Doxorubicin +exenatide (1 mcg/kg/day)	60.2±9.4**	1165.7±134.3**	-1119.9±119.4**	232±29.4
Doxorubicin +exenatide (10 mcg/kg/day)	76.8±7.4*	1302±169.2*	-1157.4±137.3*	231±26.9
Doxorubicin + vildagliptin 0.02 mg/kg/day	59.1±10.7**	1107.7±154.3**	-984.9±129.1**	227±29.4
Doxorubicin + vildagliptin 0.2 mg/kg/day	73.2±5.1*	1219±145.4*	-1108±169.3*	232±36.1

Note: LVL – left ventricular pressure (mmHg); $+ dp/dt_{max}$ – maximum contraction rate (mmHg/sec); $-dp/dt_{max}$ maximum relaxation rate (mmHg/sec); HR – heart rate (bpm). Doxorubicin was administered intraperitoneally 48 hours before the experiment. The incretin mimetics – exenatide and vildagliptin – were administered twice at an interval of 24 hours, respectively intramuscularly and intrahepatically. ** – p <0.005 in comparison with the group of intact animals *- p <0.005 in comparison with the control group.

The ability of exenatide and vildagliptin to prevent damage to cell membranes was assessed by the change in the activity of CPK-MB and LDH in the perfusate during the reperfusion period (Figure 2, 3).

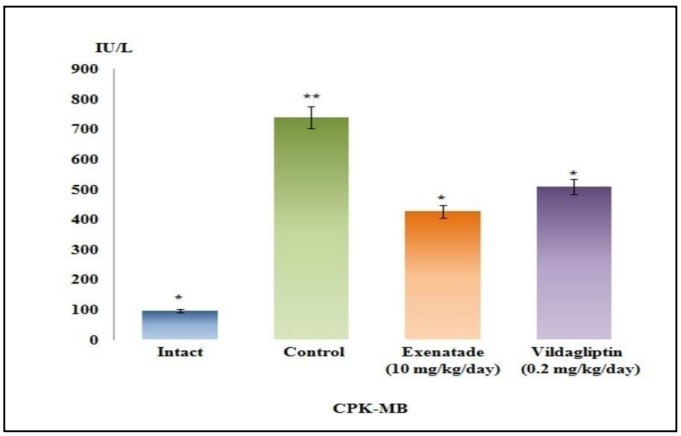


Fig. 2. Content of creatine phosphokinase in the perfusate in groups under Exenatide (10 mcg/kg/day) and Vildagliptine (0.2 mg/kg/day) on the background of Doxorubicin myocardiopathy. * p< 0.05 in comparison with the control. ** – p< 0.05 in comparison with the group of intact animals.

Exenatide and vildagliptin contributed to a decrease in CPK-MB content by 45% and 30%, and in LDH – 36% and 24% compared to the control group.

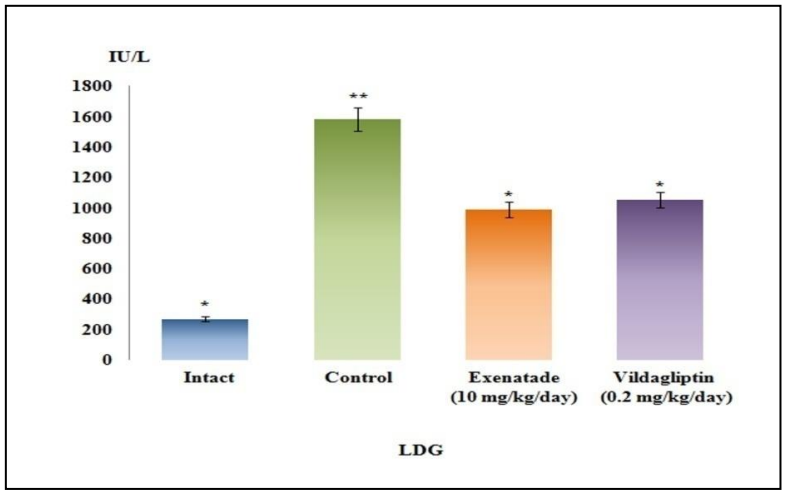


Fig. 3. Content of lactate dehydrogenase in the groups under Exenatide (10 mcg/kg/day) and Vildagliptine (0.2 mg/kg/day) on the background of Doxorubicin myocardiopathy. * – p< 0.05 in comparison with the control. ** – p< 0.05 in comparison with the group of intact animals

Similar changes were observed in the markers of products of lipid peroxidation (Figure 4, 5).

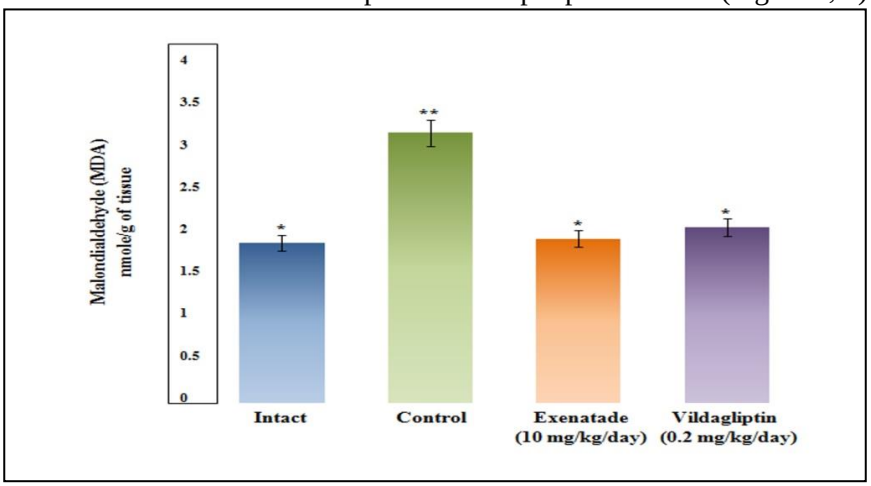


Fig. 4. Content of malonic dialdehyde in the groups under Exenatide (10 mcg/kg/day) and Vildagliptine (0.2 mg/kg/day) on the background of Doxorubicin myocardiopathy. * – p< 0.05 in comparison with the control. ** – p< 0.05 in comparison with the group of intact animals

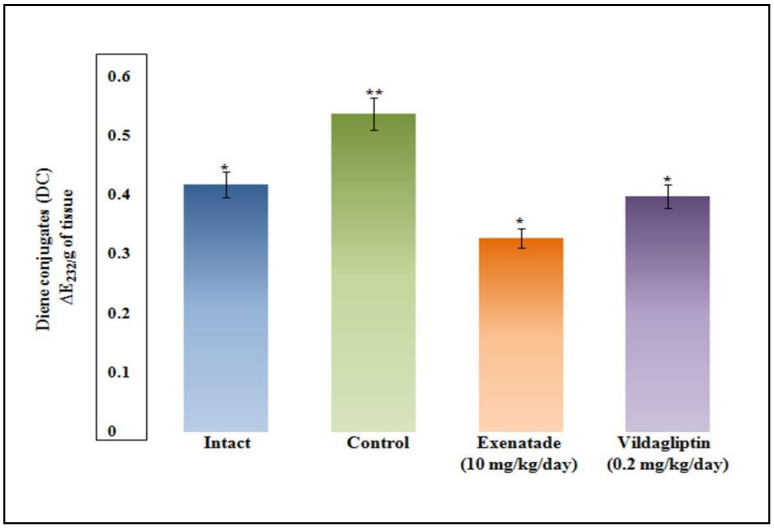


Fig. 5. Content of diene conjugates in the groups under Exenatide (10 mcg/kg/day) and Vildagliptine (0.2 mg/kg/day) on the background of Doxorubicin myocardiopathy.* – p< 0.05 in comparison with the control. ** – p< 0.05 in comparison with the group of intact animals

The formation of a highly active hydroxyl radical in the Huber-Weiss reaction involving superoxide dismutase and ferrous ions is one of the presumed causes of doxorubicin cardiomyopathy [25]. By influencing the exchange of iron: anthracyclines bind to Fe^{2+} ions, which leads to the formation of a hydroxyl radical, and promotes the release of Fe^{2+} ions from ferritin, further exacerbating oxidative stress [26].

Therefore, if the conditions for chelation or oxidation of ferrous ions Fe^{2+} in the catalytically inactive state of Fe^{3+} ions arise in the cytoplasm of cells, this will create the conditions for achieving micromolar concentrations of reactive oxygen species (ROS) in the cytoplasm of cells and reducing the damage to cardiomyocytes [27]. From the pharmacological point of view, antioxidants are of interest as one of the promising groups of cardioprotective drugs that allow to preserve a viable myocardium, limit the size of damage and accelerate the restoration of contractile activity of the myocardium [28, 29].

In incretins, the presence of one of the ways of realization of cardioprotective effect is described – the amplification of expression of heme-oxygenase-1 (HO-1) [30]. This enzyme prevents the heme-catalyzed formation of highly active hydroxyl radicals from hydrogen peroxide. Activation of heme-oxygenase-1 is associated with increased heme catabolism to bile pigments, which are potential endogenous antioxidants. In addition, induction of heme-oxygenase-1 is accompanied by an increase in ferritin activity, which has an antiapoptotic effect [31]. The enhancement of expression of heme-oxygenase-1 under conditions of oxidative stress can play an adaptive role in response to oxidative damage and diminish the death of cardiomyocytes.

The experimental studies demonstrate that when dosorubicin-induced cardiomyopathy is modeled in transgenic mice and animals with overexpression of HO-1, cardiac-specific hyperexpression of HO-1 prevents doxorubicin-mediated damage of sarcoplasmic reticulum and mitochondria in autophagic vacuoles [32]. Overexpression of HO-1 promotes mitochondrial biogenesis by enhancing the expression of the protein of the nuclear respiratory factor (NRF1), the coactivator (PGC1α) and the mitochondrial transcription factor (TFAM) that are inhibited in transgenic animals with doxorubicin-induced cardiomyopathy. Simultaneously, overexpression of HO-1 inhibits the enhancement of the mitochondrial fusion mediator (Fis1) and leads to an increase in the expression of the mediators of the synthesis of Mfn1 and Mfn2. This also prevents mutations in key mitochondria genes PINK1 and PARKIN and ensures their normal functioning. This proves that NO-1 plays an important role in protecting the heart from oxidative damage by affecting mitochondria [33]. It can be surmised from the above that the mechanisms of antioxidant defense expression may take part in the mechanism of the protective action of the incritinomimetics in doxorubicin myocardiopathy.

Conclusion.

Thus, the incretin mimetics exenatide (10 mcg/kg/day) and vildagliptin (0.2 mg/kg/day) in the doxorubicin cardiomyopathy model have a protective effect, which manifests itself in the prevention of development of the "diastole defect" in the high-frequency cardiac stimulation of the isolated heart of rats, in a dicrease in the levels of CPK-MB and LDH damage markers, as well as in prevention of

accumulation of lipid peroxidation products of MDA and DC in the ventricular myocardium.

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

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