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CARDIOTROPIC PROPERTIES OF CHROMONE-3-ALDEHYDE DERIVATIVES UNDER AN EXPERIMENTAL CARDIAC INFARCTION COMPLICATED WITH HYPERCHOLESTEROLEMIA

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Cardiac infarction still remains a leading cause of mortality among population. There are a lot of risk factors causing the disease and complicating it; undoubtedly, they require correction. Our research goal was to experimentally assess cardiotropic peculiarities of 4 chromone-3-aldehyde derivatives (coded as X3AF, X3AFOK, X3ANO₂, and X3ANO₂OK) as medications aimed at minimizing risks of acute cardiac infarction complicated with hypercholesterolemia. The experiment was performed on 70 male Wistar rats (pubescent, with body weight being equal to 220-240 grams); the animals were divided into 7 equal experimental groups, 10 animals in each. The first group was made up of falsely operated animals. We modeled atherogenesis in 60 remaining rats via oral introduction of 3 % cholesterol dissolved in sunflower oil; the solution was introduced daily for 14 days. We also modeled acute cardiac infarction in them via ligating the left descending coronary artery with a silk thread. After 24 hours we performed electrocardiography to assess changes in QT range, and P, R, and T peaks amplitude. We also determined sizes of necrosis zones and ischemic damage foci in the cardiac muscle via double dying with Evans blue and tetrazolium chloride. We detected that compounds encoded as X3ANO₂, X3ANO₂OK, X3AF and X3AFOK had hypocholesteremic and cardiotropic effects which led to electrophysiological properties returning to physiological standards and a decrease in ischemia/necrosis zones in the cardiac muscle under cardiac infarction. Objects encoded as X3ANO₂OK and X3AFOK were more pharmacologically active than X3ANO₂ and X3AF, and X3ANO₂OK substance was comparable to a reference medication, Meldonium in our case, in terms of its activity. Overall, the examined substances can be considered medications able to minimize risks of acute cardiac infarction complicated with hypercholesterolemia.

Key words: hypercholesterolemia, cardiac infarction, population mortality, risk factors, ischemia, necrosis, chromone derivatives, Meldonium, cardiac hystiocytes.

Despite all the successes that have been achieved in contemporary cardiology, mortality caused by cardiac infarction and its complications tends to grow. According to the WHO forecasts, by 2025 death cases caused by cardiac infarction are expected to rise from 17 million to 25 million annually [1, 2]. It's

common knowledge, that cardiac infarction means death of cardiac muscle cells (cardiac myocytes) that results from insufficient oxygen supply to the cardiac muscle, or cardiac muscle ischemia [3], and cardiac muscle cells start to die more than 6 hours after ischemia occurs [4]. Cardiac infarction develops due to

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several factors, primary ones being hyperlipidemia and atherosclerosis, hyperglycemia, smoking, arterial hypertension, alcoholism [5]. Besides, such factors as endothelial dysfunction, inflammation in vascular walls, cytokine cascade, and apoptosis [6] also make a significant contribution into cardiac infarction occurrence as they initiate damages in the cardiac muscle.

All the existing therapeutic strategies aimed at treating cardiac infarction are combinations of pharmaceutical, therapeutic, and instrumental techniques and "stent-technologies" [7] that are usually quite efficient. Their application allows to decrease mortality caused by acute cardiac infarction phase [8]. However, complications (mechanic, arrhythmic, ischemic, and inflammatory ones) that usually accompany cardiac infarction on the contrary make mortality among patients increase and it causes substantial health risks for population [9]. Given all the above stated, cardiac infarction prevention and risk factors elimination can be considered one of the most important tasks in contemporary medicine. Cardioprotectors are a pharmacological-therapeutic group of medications that exert favorable impacts on cardiac muscle functions and are predominantly aimed at prevention. Such medications can have direct and indirect effects [10]. Cardioprotectors with direct effects, or myocardial cytoprotectors, are the most promising; their action mechanism is directly aimed at recovering functions and stabilizing cell membranes, including mitochondria and lysosomes membranes [11]. This effect is pleiotropic when it comes to indirect cardioprotectors. At present, there are more than 2,000 molecules that can potentially have cardioprotecting properties, but much fewer compounds have been actually introduced into clinical practices and it calls for targeted searching for cardiotropic medications with multi-target action mechanism aimed at stabilizing cardiac muscle functioning and risk factors elimination [12].

Our research goal was to experimentally assess cardiotropic properties of chromone-3-aldehyde derivatives as medications that could

minimize risks of acute cardiac infarction complicated with hypercholesterolemia.

Data and methods. We performed our experimental research on 70 male Wistar rats (pubescent, with body weight being equal to 220–240 grams); the animals were divided into 7 experimental groups, 10 rats in each. The first group was falsely operated animals (FOA). We modeled atherogenesis in 60 remaining rats via oral introduction of 3–5 cholesterol solution in sunflower oil (Pancreac, Spain); the solution was introduced daily during 14 days [13]. The second group of rats was negative control (NC) as animals from this group didn't receive any pharmaceutical support. Animals from the third group were given a reference medication, Meldonium (Mildronate, Grindex (Latvia)) in a dose equal to 90 mg/kg [14]. The 4th, 5th, 6th, and the 7th group of rats were given new chromone-3-aldehyde derivatives encoded as X3AF, X3AFOK, X3ANO₂ и X3ANO₂OK respectively in a dose equal to 20 mg/kg. All the examined medications and the reference one were daily introduced *per os* during 14 days, along with cholesterol introduction (there was a 2-hour break between two introductions), animals from NC group were given 0.9%-sodium chloride solution in the same dose. When 14 days passed, we modeled acute cardiac infarction (ACI) in all the rats (including falsely operated animals who had undergone all the above-mentioned procedures, apart from coronary artery ligation) via ligating the left descending coronary artery with silk thread under chloral hydrate (350 mg/kg) anesthesia [14].

We performed electrocardiography 24 hours after ligation to monitor the experimental animals in the II standard lead with «Poly-Spectr-8/B» electrocardiograph (Nuerosoft, Russia) with assessing changes in QT range, P, R, and T waves. We also determined sized of necrosis zones and an ischemic damages focus in the cardiac muscle; to do that, we applied double dying with Evans blue and tetrazolium chloride (Figure 1) [15].

In order to examine probable favorable impacts exerted by the examined substances on lipid and lipoprotein blood profile, we assessed

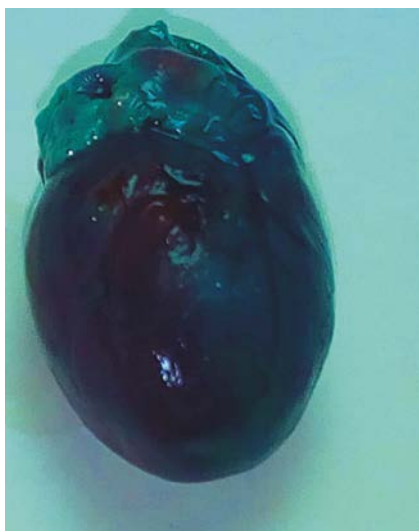


Figure 1. Double dyeing of the cardiac muscle with Evans blue and tetrazolium chloride obtained in the research

(after ACI had been modeled) changes in concentrations of total cholesterol (TC), low-density lipoproteins (LDLP cholesterol, LDLPC), high-density lipoproteins (HDLP cholesterol, HDLPC), and triglycerides (TG) in blood serum of the experimental animals (to do that, we applied standards reagent kits «Olveks Diagnosticum»). Samples preparation and analysis procedures conformed to the instructions given by a manufacturer of each reagent kit.

Experimental results were statistically processed with STATISTICA 6.0 package (StatSoft, the USA). Statistically significant

discrepancies between groups of mean values were determined with «AVONA» technique together with Newman-Keuls post-test with significance level being $p < 0.05$.

Results and discussion. We assessed lipid and lipoprotein blood structure and detected that 14-day introduction of 3% cholesterol solution in sunflower oil led to an increase in concentrations of total cholesterol, LDLP cholesterol, and TG (Table 1) in rats from the negative control group against falsely operated animals as these concentrations were by 54.3% ($p < 0.05$), 86.2% ($p < 0.05$), and 35.1% ($p < 0.05$) higher in them respectively; as for HDLP cholesterol, it was by 43.8% lower in NC animals, than in falsely operated ones ($p < 0.05$).

Application of Meldonium under experimentally induced atherogenesis promoted lipid metabolism recovery (table 1) as it became apparent via a decrease in concentrations of TC, LDLPC, and TG in blood plasma of rats that were given Meldonium against animals from the negative control group; these concentrations were by 46.2% ($p < 0.05$), 48.6% ($p < 0.05$), and 28.3% ($p < 0.05$) lower respectively in the former group than in the latter one; HDLPC was also by 35.9% higher among rats which were given Meldonium than among animals from the negative control group ($p < 0.05$).

We assessed impacts exerted by the examined substances on lipid-lipoprotein blood profile and analyzed the results; the analysis

Table 1

Influence exerted by the examined substances and the reference medication on changes in lipid and lipoprotein blood profile under experimentally induced hypercholesterolemia

Group	Total cholesterol, mmol/l	LDLP cholesterol, mmol/l	HDLP cholesterol, mmol/l	Triglycerides, mmol/l
FOA	2,34 ± 0,1	1,38 ± 0,067	0,92 ± 0,033	0,57 ± 0,016
NC	3,61 ± 0,126#	2,57 ± 0,177#	0,64 ± 0,029#	0,77 ± 0,014#
Meldonium	2,47 ± 0,126*	1,73 ± 0,082*	0,87 ± 0,018*	0,60 ± 0,027*
X3ANO ₂	2,89 ± 0,03*	2,11 ± 0,054*	0,73 ± 0,025*	0,64 ± 0,013*
X3ANO ₂ OK	2,37 ± 0,054*	1,81 ± 0,026*	0,79 ± 0,022*	0,61 ± 0,006*
X3AF	2,51 ± 0,032*	2,35 ± 0,047	0,77 ± 0,025*	0,64 ± 0,011*
X3AFOK	3,0 ± 0,051*	2,08 ± 0,075*	0,72 ± 0,032*	0,67 ± 0,006*

Note: # means a value is statistically significant against falsely operated animals ($p < 0.05$); * means a value is statistically significant against the negative control group ($p < 0.05$).

revealed that X3ANO₂ and X3AFOK led to practically the same changes in all the examined parameters (Table 1). Thus, X3ANO₂ and X3AFOK application led to 24.9% (p<0.05) and 20.3% (p<0.05) decrease respectively in TC concentration (against the NC group); LDLPC was also lower (by 21.8% (p<0.05) and 23.6% (p<0.05) respectively); TG concentration was by 20.3% (p<0.05) and 15% lower respectively. On the contrary, HDLPC concentration was higher after X3ANO₂ and X3AFOK introduction than in animals from the negative control group, by 14% (p<0.05) and 12.5% (p<0.05) respectively.

X3AF introduction led to lower TC and TG concentrations in rats' blood plasma against the NC group, by 43.8% (p<0.05) and 20.3% (p<0.05) respectively. On the contrary, HDLPH concentration was by 20.4% higher after the substance was introduced (against the NC group) (p<0.05). After X3ANO₂OK was introduced, we detected lower concentrations of TC, LDLPC, and TG, as well as higher HDLPC concentration in rats' blood plasma, by 52.3% (p<0.05), 42% (p<0.05), 26.2% (p<0.05), and 23.4% (p<0.05) respectively.

We assessed changes in bioelectric parameters of heart functioning (Table 2) when acute cardiac infarction occurred and detected that P and T waves amplitudes were 3 (p<0.05) and 6 (p<0.05) times greater respectively in animals from the negative control group against falsely operated ones, and QT interval was by

87.8% longer in them. Besides, R wave amplitude was 3.3 times (p<0.05) smaller in rats from the negative control group against falsely operated animals and these data are consistent with literature [16]. Preventive introduction of Meldonium resulted in favorable dynamics of changes in cardiac muscle electrophysiology in rats under cardiac infarction as P wave amplitude and QT interval length were 2 times (p<0.05) and by 68.7% (p<0.05) lower respectively against animals from the negative control group, and R wave amplitude was 3.2 times greater (p<0.05).

Introduction of the examined substances X3ANO₂, X3ANO₂OK, X3AF, and X3AFOK led to an increase in R wave amplitude against animals from the negative control group, by 83.3% (p<0.05); 166.7% (p<0.05); 133.3%, and 216.7% (p<0.05) respectively. Besides, when X3ANO₂, X3ANO₂OK, and X3AFOK were introduced, it resulted in a decrease in QT interval against the NC group by 38.5% (p<0.05); 127.9% (p<0.05), and 51.6% (p<0.05) respectively. T wave amplitude went down by 33.3% (p<0.05) against the NC group after X3ANO₂OK introduction.

We analyzed data obtained in assessing changes in sizes of ischemia/necrosis zones in the cardiac muscle and revealed that Meldonium introduction led to a decrease in sizes of both ischemia and necrosis foci against the NC group, by 59.9% (p<0.05) and 52.7% (p<0.05) respectively (Figure 2).

Table 2

Influence exerted by the examined substances and the reference medication on changes in bioelectric parameters of heart functioning under acute cardiac infarction combined with experimentally induced hypercholesterolemia

Group	P, millivolt	R, millivolt	T, millivolt	QT, ms
FOA	0,02 ± 0,004	0,2 ± 0,027	0,04 ± 0,01	81,11 ± 6,127
NC	0,06 ± 0,004#	0,06 ± 0,017#	0,24 ± 0,027#	152,36 ± 3,269#
Meldonium	0,03 ± 0,005	0,19 ± 0,013*	0,2 ± 0,007	90,33 ± 4,235*
X3ANO ₂	0,04 ± 0,002	0,11 ± 0,011*	0,2 ± 0,015	110,04 ± 9,783*
X3ANO ₂ OK	0,04 ± 0,004	0,16 ± 0,01*	0,18 ± 0,009*	66,85 ± 2,459*
X3AF	0,02 ± 0,002	0,14 ± 0,005*	0,21 ± 0,009	139,12 ± 3,297
X3AFOK	0,03 ± 0,004	0,19 ± 0,013*	0,23 ± 0,022	100,5 ± 1,269*

Note: # means a value is statistically significant against falsely operated animals (p<0.05); * means a value is statistically significant against the negative control group (p<0.05).

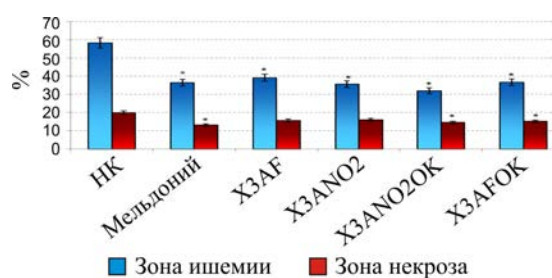


Figure 2. Changes in sizes of ischemia/necrosis zones in the cardiac muscle when correcting cardiac infarction complicated hypercholesterolemia with the examined substances and Meldonium

Note: # means a value is statistically significant against falsely operated animals ($p < 0.05$); * means a value is statistically significant against animals from the NC group ($p < 0.05$).

After the examined substances X3ANO₂, X3ANO₂OK, X3AF, and X3AFOK were applied, sizes of ischemic damage zone in the cardiac muscle decreased against the NC group, by 63.7% ($p < 0.05$); 82% ($p < 0.05$); 48.8% ($p < 0.05$), and 59.1% ($p < 0.05$) respectively.

A necrotic focus decreased in sizes statistically significantly against animals from the NC group after X3ANO₂OK and X3AFOK had been introduced, by 37.7% ($p < 0.05$) and 32.3% ($p < 0.05$) respectively.

Such cardiotropic effects produced by chromone-3-aldehyde derivatives can be due to their anti-cytokine properties. Chromone derivatives are known to be able to suppress occurrence of tumor necrosis factor- α (TNF- α) [17]. TNF- α activates external apoptosis path, and, in case of cardiac infarction, it promotes greater necrotic foci and, as a result, systolic functions performed by the left ventricle dete-

riorate substantially [18]. Besides, greater TNF- α concentration leads to inflammation cascade development and fibrosis in the cardiac muscle thus exerting adverse impacts on the disease course [19]. Favorable effects produced by the examined chromone derivatives on lipid metabolism can be related to their regulatory capabilities as regards sirtuin proteins [20] that play an important role in metabolic reactions of lipoproteins, fat acids, and dextrose [21].

Conclusion. Our research revealed that new chromone-3-aldehyde derivatives had cholesterol-lowering and cardiotropic effects. Cholesterol-lowering effects produced by the examined substances became apparent as lipid-lipoprotein blood profile returned to its physiological standards while their cardiotropic effects assessed under modeled cardiac infarction complicated with hypercholesterolemia promoted recovery of electrophysiological properties and decrease in sizes of ischemia/necrosis zones in the cardiac muscle. All the obtained data allowed us to assume that X3ANO₂OK and X3AFOK substances were more pharmacologically active than X3ANO₂ and X3AF. The research object encoded as X3ANO₂OK has pharmacological properties comparable to those of Meldonium, which was the reference medication in the research. Overall, these substances can be considered medications aimed at minimizing risks of acute cardiac infarction complicated with hypercholesterolemia.

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