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The Inotropic Effects of 3'4'-Dimetyl Quercetin in Isolated Rat Papillary Muscle*

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Abstract

The aim of the present study was to determine the inotropic effect of 3'4'-dimethyl quercetin in the rat myocardium. Isometric tension forces were recorded using a force transducer (Type F30/Model D-79232; Hugo Sachs Elektronik, March-Hugstetten, Germany). 3',4'-dimethyl quercetin (10–100 μmol·L^{-1}) exerts a positive inotropic effect in rat papillary muscles. Thus, inhibitor potential-dependent $Ca^{2+}{}_L$-channels – nifedipine and inhibitor β-adrenoreceptor – propranolol has almost completely abolished the positive inotropic effects of 3',4'-dimethyl quercetin. Moreover, it was identified that the 3',4'-dimethyl quercetin depending on dose has increased quantity of the maximum velocity of force development, and the maximum velocity of papillary muscles relaxation. In conclusion, the present study demonstrates that 3',4'-dimethyl quercetin has showed a positive inotropic effect on rat papillary muscles that can be explained with the increase of $[cAMP]_{in}$ and may depend on increase of $[Ca^{2+}]_{in}$. Furthermore, lusitropic effect of 3',4'-dimethyl quercetin can be increased in cAMP and inhibition of phosphodiesterase enzyme activates protein kinase A, which phosphorylates regulator protein activity Ca^{2+}-ATPase – phospholamban and RyRs.

Keywords: papillary muscles, inotropic effect, 3',4'-dimethyl quercetin

Introduction

Nowadays, in pharmaceutical industry researches find cure against many various diseases, the direction of tendency is observed towards the growth of interest to search and create medical products based on bioflavonoids. Development of this field depends on having many advantageous

Abbreviations: AC – adenylate cyclase; ATP – adenosintriphosphat; $Ca^{2+}{}_L$-channels – the L-type Ca^{2+}–channels; $[cAMP]_{in}$ – the intracellular concentration of cyclic adenosine 3',5'–monophosphate; $[Ca^{2+}]_{in}$ – the intracellular concentration of Ca^{2+} ions; $+dF/dt_{max}$ – the maximum velocity of force development; $-dF/dt_{max}$ – the maximum velocity of relaxation; DMSO – dimethyl sulfoxide; EC_{50} – values of concentration for 50% of the maximal effect; Gs – guanine nucleotide-binding proteins; HSE – Hugo Sachs Elektronik; PKA – protein kinase A; SR – sarcoplasmic reticulum; RyRs – ryanodine receptors or sarcoplasmic reticulum Ca^{2+}–channels; CICR – "Ca^{2+} induced Ca^{2+} release"; SERCA – Ca^{2+}–ATPase of sarcoplasmic reticulum; $T_{contr.}$ – time from peak tension; $T_{1/2\ relax.}$ – time from to 50% relaxation.

pharmacological viewpoints of flavonoids. For example when bioflavonoids are utilized with other preparations, they will have pharmacological influence in wide spectrum with low toxicity, in addition to this it is identified that very seldom side effect occurred while practical absence of contra–indications.

Many flavonoids have low toxic influence on mammals and they show wide range of pharmacological influence and bioflavonoids are supposed to have a great therapeutic potential [1, 2]. According to previous experiments, flavonoids have a numerous valuable pharmacological impacts, such as cardiotonic, anticancer [3, 4], anti–atherosclerotic, antiproliferative, antiplatelet, antihypertensive [5], anticonvulsant, antibacterial and prophylactic effective preparations in various vascular diseases [2]. Many plant types containing flavonoids have been used in traditional Oriental medicine for thousands of years [6].

The flora of Central Asia is well known with very rich flora and various medical plants [7]. Moreover, scientists of Institute of the Chemistry of Plant Substances of Academy of Sciences of the Republic of Uzbekistan have extracted bioflavonoids from local plants [8, 9]. However, their mechanisms of pharmacological impact have not been studied yet. Therefore, the aim of the present study was to identify the possible mechanisms of the inotropic effect of 3',4'-dimethyl quercetin on the rat papillary muscle.

Material and methods

Animals and Ethics statement. This study was carried out in the Laboratory of Electrophysiology of Institute of Bioorganic Chemistry of Academy Sciences of the Republic of Uzbekistan on physically fit, adult, albino rats in both sexes (female and male) obtained from the vivarium in the Laboratory of Pharmacology. Animals had been fed with standard food and water in the vivarium. In all experiments albino rats weighing 200–250 g were used (n = 18). During the experiments, while working with experimental animals, International principles of the Helsinki Declaration and the rules of human attitudes towards animals were completely followed.

Solvents and chemicals. All reagents, which were used in experiments, were of analytic–grade (NaCl, KCl, $CaCl_2$, $MgSO_4$, KH_2PO_4, glucose, $NaHCO_3$), (±)-propranolol hydrochloride, prazosin, nifedipine hydrochloride, phentolamine, dimethyl sulfoxide (DMSO) were obtained from Sigma Chemical (St. Louis, Missouri, USA). 3',4'-dimethyl quercetin was produced from plants by scientists of the Institute of the Chemistry of Plant Substances of Academy Sciences of the Republic of Uzbekistan and presented by PhD Diloram ALIMOVA (Figure 1).

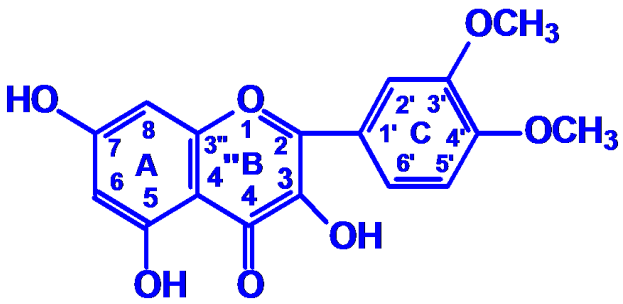

Figure 1. Chemical structure of 3',4'-dimethyl quercetin

3',4'-Dimethyl quercetin was categorized as a flavonol according to its structural complexity [6]. 3',4'-dimethyl quercetin and nifedipine hydrochloride were dissolved in dimethyl sulfoxide (DMSO). The final concentration of DMSO did not surpass 0.1% under incubation condition and DMSO did not have any effect on the contractility of isolated papillary muscles preparations when added alone at a concentration of 0.1%. (±)-Propranolol hydrochloride was dissolved in deionized water in a concentration of 10 μmol·L^{-1}.

Preparation of tissue and measurement of contractility and setup of the equipment. The prepared papillary muscle was connected to a force transducer for signal recording. In experiments the papillary muscles preparations, isolated from the right atrium of adult albino rats' hearts. Rats were deeply anaesthetized with diethyl prior to paralyzing by using

cervical dislocation method. The papillary muscles were, 0.4–1.3 mm in diameter and 2.5–3.8 mm in length. The papillary muscles samples were prepared according to Sonnenblick (1964) [10], and the muscle was placed in an special horizontal tissue chamber (Type 813; Hugo Sachs Elektronik, March-Hugstetten, Germany), designed for the *in vitro* study in standard pharmacological experiments for measuring contraction force response of papillary muscle preparations. The top of the system was open and it is provided with the organ chamber, volume of 5 ml, the thermo–circulator for flow heater physiological solution and the wire holder for the force transducer (Type F30/Model D-79232; Hugo Sachs Elektronik, March-Hugstetten, Germany), with a precision micrometer control. In the experiments, modified the physiological Krebs–Henseleit solution containing (in mM): 118 NaCl; 4.7 KCl; 2.5 $CaCl_2$; 1.2 $MgSO_4$; 1.1 KH_2PO_4; 5.5 glucose and 25 $NaHCO_3$; pH 7.4 were used. This Krebs–Henseleit solution which was continuously bubbled with 95% O_2 and 5% CO_2 and kept at a temperature of +36±0.5 °C by means of water heating system controlled by temperature controller U8 (Bulgaria), and flowed in and out of the organ bath at a rate of 3–5 ml/min with the peristaltic pump LKB Bromma (Sweden).

The Isometric force transducer F30 is connected to a transducer amplifier (Type TAM-A; Hugo Sachs Elektronik, Harvard Apparatus GmbH, Germany). The papillary muscle was lifted with electric impuls that was higher than threthold (~20%), rectangular, electrical pulses of frequency 0.5 Hz; 5 ms and 5 V amplitude, delivered via a pair of platinum electrodes placed in the muscle–mounting organ chamber by using stimulator ESL–2 (Russia). Thus, wires of a pair of platinum electrodes were placed as parallel to the organ; the physiological solution of Krebs–Henseleit provides shortening the electrical contact distance between the electrodes and the preparate of the papillary muscles. In this experiment, 10 mN (1 g ~ 9.8 mN) was accepted for a resting tension of the preparation papillary muscles. After a 60 minute equilibration period, the length that provides development of the maximal isometric contractile force (L_{max}, the maximal length) length of the papillary muscle was found, and all experiments were carried out in these condition. After the equilibration period in the organ chamber, papillary muscles were stimulated by an initial electrical pulse of frequency 0.5 Hz, amplitude 5 V, and 5 msec pulses. The signals obtained were given from the transducer F30 to amplifier and sent to a computer by using a pen chart recorder (Type TZ 4620; Czech Republik) or a personal computer with analogue-digital converter LabPro Logger Lite 1.2 software (Vernier Software & Technology, Beaverton, USA).

In this experiments, the maximum velocity of force development ($+dF/dt_{max}$), and maximum velocity of relaxation ($-dF/dt_{max}$) of papillary muscles data were saved and analysed by means of specially software [11] running on a IBM PC computer interfaced with a D/A converter.

Data analysis. Papillary muscle contractions were plotted as a percentage of the force before the drug application in each muscle. Data were analyzed by OriginPro 7.0 (MicroCal Software, Northampton, MA). Pooled data are given as means ±S.E.M. of observations (n). Concentration–response curves were fitted to the logistic equation: $E = E_{\max} /(1+10^{-k\times([drug]-pD_2)})$, where E_{max} – is the maximal effect, k – is a factor which represents the slope of the curve, and pD_2 – is the drug concentration exhibiting 50% of the E_{max} expressed as negative log molar [12]. Values are expressed as mean ±S.E.M. Statistical differences of the data were calculated by ANOVA and the paired or unpaired Student's t–test where appropriate. The values were considered significantly different when $p<0.05$.

Results

The positive inotropic effects of 3',4'-dimethyl quercetin on rat myocardium. In the experiments, the 3',4'-dimethyl quercetin was added to the organ bath as the following concentration range: from 1 μmol·L⁻¹ to 100 μmol·L⁻¹ and doses were considered as the answer. Then 3',4'-dimethyl quercetin did not show inotropic effects at low concentrations (1–5 μmol·L⁻¹), and positive inotropic effects of 3',4'-dimethyl quercetin started to appear at concentrations 10 μmol·L⁻¹. And 3',4'-dimethyl quercetin (10–100 μmol·L⁻¹) showed dose-dependent positive inotropic effects (PIE) in rat papillary muscle contractility. Figure 2 shows the original recordings inotropic influence of 3',4'-dimethyl quercetin at 100 μmol·L⁻¹ concentration on the papillary muscle isometric contraction force (Figure 2).

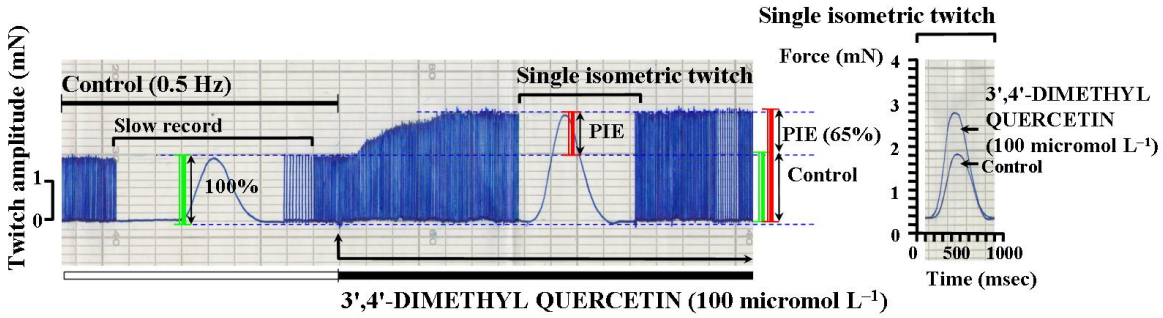

Figure 2. Original recordings of positive inotropic effect of 3',4'-dimethyl quercetin on a rat papillary muscle. Stimulation: 0.5 Hz with pulses of amplitude 5 V, and 5 msec (+36±0.5 °C)

The condition where the maximal effected concentration (100 μmol·L⁻¹) of 3',4'-dimethyl quercetin, the isometric developed force of papillary muscle preparation was increased from 2.345±0.1 mN (the control basal value) to 3.923±0.2 mN or 67.31±5.2% in comparison with the control group ($P < 0.05$; n=4). In these conditions, the EC_{50} value (the values of concentration for 50% of the maximal effect) of 3',4'-dimethyl quercetin was 13.8 μmol·L⁻¹or pD_2 ($-\log EC_{50}$) = 4.86.

Role of potential-dependent $Ca^{2+}{}_L$-channels and adrenergic receptors in the inotropic effects of 3',4'-dimethyl quercetin. Studies have shown that in incubation to inhibit potential-dependent Ca^{2+}-channel – nifedipine (0.01 μmol·L⁻¹) the positive effect of 3',4'-dimethyl quercetin decreases to 21.4±3.6% of control values (Figure 3).

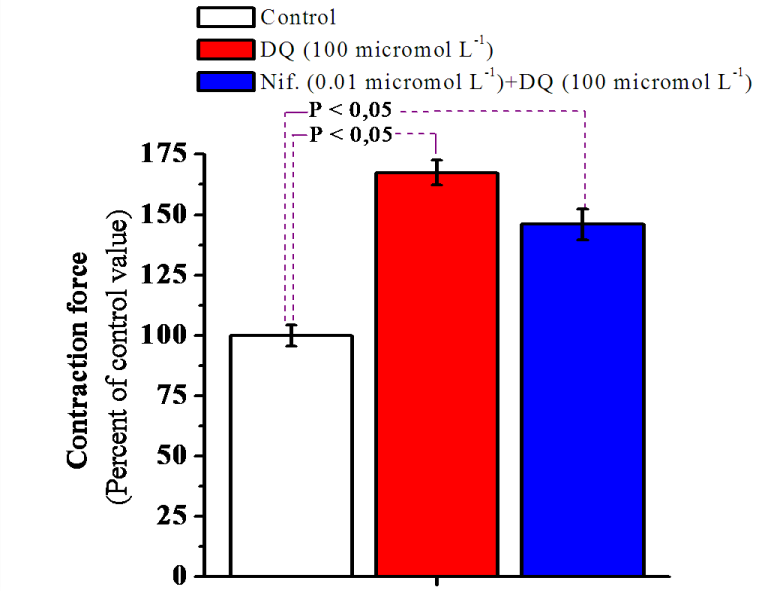

Figure 3. Comparison of the inotropic effects of 3',4'-dimethyl quercetin and nifedipine on the contraction force of extracted rat papillary muscle. Stimulation: 0.5 Hz, 5 V, 5 msec, +36±0.5 °C, resting tension = 10 mN. Data shown for 3',4'-dimethyl quercetin (DQ) (100 μmol·L⁻¹) and nifedipine (Nif.) (0.01 μmol·L⁻¹) were presented as means ± of 4 experiments. $P < 0.05$ indicates value compared to control

The results of experiment demonstrate that the positive inotropic effect of 3',4'-dimethyl quercetin on papillary muscle is not completely connected with potential-dependent $Ca^{2+}{}_L$-channel cardiomyocytes.

It is known that phentolamine and prazosin are inhibitors of α-adrenergic receptors and they reduce the positive inotropic effect of α-adrenergic receptors agonists at the papillary muscle which was extracted under higher concentrations [13]. In the experiment, the inhibitor of α-adrenergic

receptors – phentolamine (5 μmol·L⁻¹) and prazosin (10 μmol·L⁻¹) did not show significant effect on the positive inotropic effect of 3',4'-dimethyl quercetin. Moreover, preincubation of the papillary muscle with phentolamine (5 μmol·L⁻¹) and prazosin (10 μmol·L⁻¹) did not influence on the positive inotropic effect of 3',4'-dimethyl quercetine (100 μmol·L⁻¹) (data is not given). The positive inotropic effect of 3',4'-dimethyl quercetin was not dependent on activation of α-adrenergic receptors.

The positive inotropic effect of 3',4'-dimethyl quercetin was considerably decreased at blocking stage of β-adrenergic receptor with (±)-propranolol hydrochloride (10 μmol·L⁻¹). Figure 4 illustrates concentration – response curves for the positive inotropic effect of 3',4'-dimethyl quercetin and (±)-propranolol hydrochloride (10 μmol·L⁻¹) on rat papillary muscles at 0.5 Hz stimulation (Figure 4).

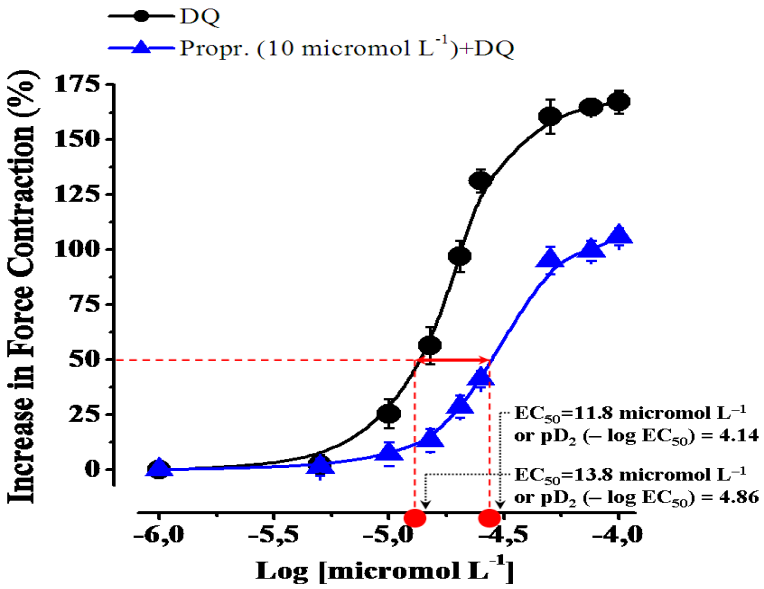

Figure 4. Concentration–response curves for the positive inotropic effects of 3',4'-dimethyl quercetin and (±)-propranolol hydrochloride. Propranolol hydrochloride (Propr) (10 μmol·L⁻¹) was added 10 min before the addition of 3',4'-dimethyl quercetin (100 μmol·L⁻¹) to the incubation. Results are given as means ±S.E.M., n = 4. Stumulation: 0.5 Hz, 5 V, 5 msec, +36±0.5 °C, resting tension = 10 mN

In addition, the positive inotropic effect of 3',4'-dimethyl quercetin was almost completely disappeared in the presence of inhibitor of potential-dependent Ca^{2+}_L-channel – nifedipine (0.01 μmol·L⁻¹) and inhibitor β-adrenoreceptor – (±)-propranolol hydrochloride (10 μmol·L⁻¹) under incubation conditions (Figure 5).

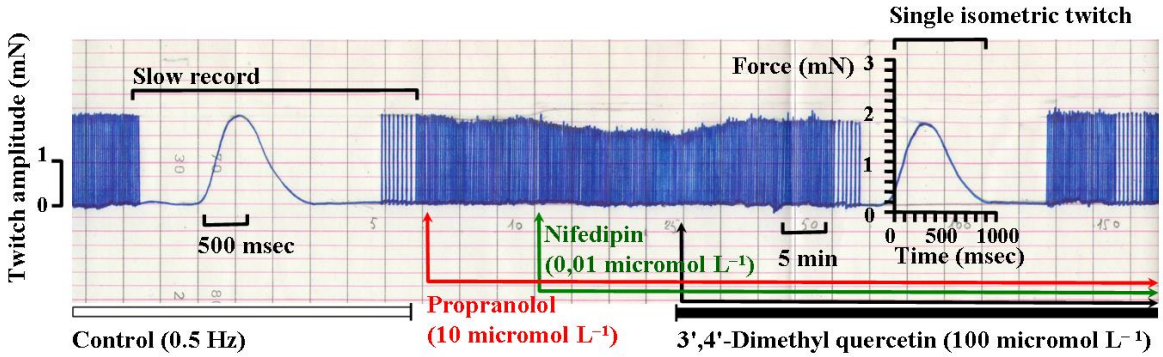

Figure 5. Original recordings for the influence of nifedipine (0.01 μmol·L⁻¹) and (±)-propranolol hydrochloride (10 μmol·L⁻¹) on positive inotropic effect of 3',4'-dimethyl quercetin in a rat papillary muscle. Stumulation: 0.5 Hz with pulses of 5 V, and 5 msec (+36±0.5 °C)

In experiments, in order to analyze the parameters of contraction and relaxation of the papillary muscles, the maximum amplitude force of isometric contraction, the maximum velocity of force development ($+dF/dt_{max}$) and the maximum velocity of relaxation ($-dF/dt_{max}$) were calculated (Figure 6).

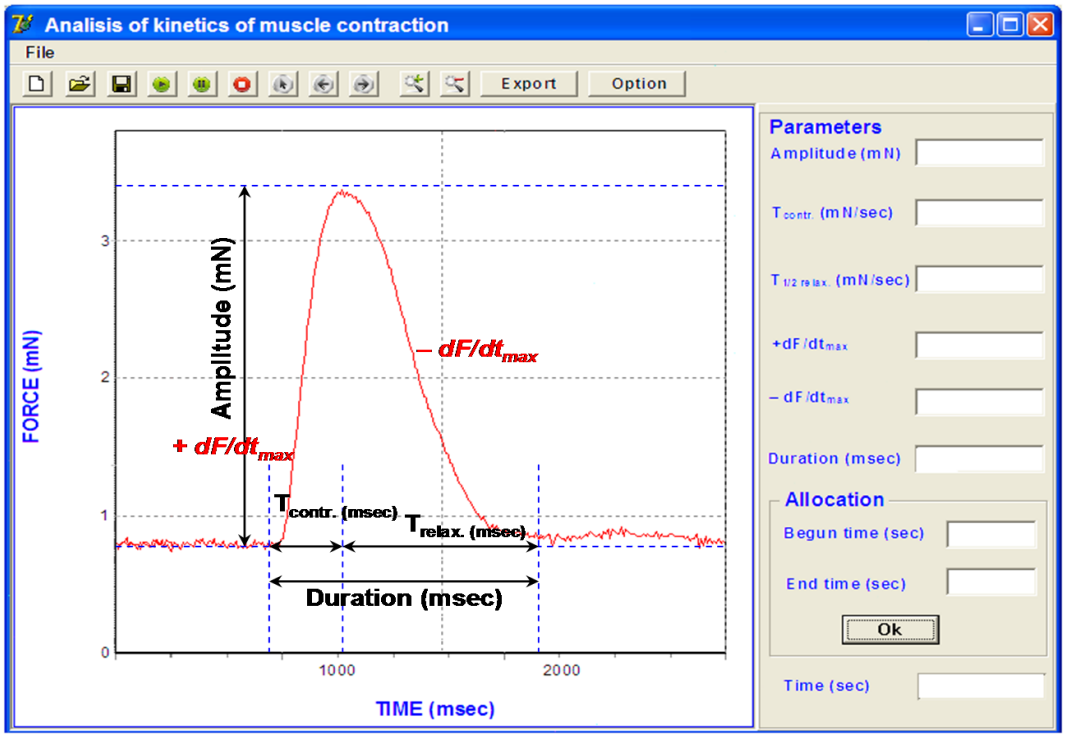

Figure 6. The parameters of single isometric contraction of the extracted rat papillary muscle of control group. This experimental report was obtained by means of the special software "Analysis of kinetics of muscle contraction", created with cooperation of Tashkent University of Information Technology [11]

The mechanical velocity parameters of papillary muscles contractile force are expressed in mN/msec. The investigation showed that 3',4'-dimethyl quercetin dose-dependent (10–100 μmol·L^{-1}) increased the maximum velocity of force development ($+dF/dt_{max}$), and the maximum velocity of relaxation ($-dF/dt_{max}$) (*lusitropic effect*) of papillary muscles (Table).

Table 1: Effect of different concentrations of 3',4'-dimethyl quercetin on the parameters of isometric contraction of the rat isolated papillary muscle of experimental and control group

Concentration of 3',4'-dimethyl quercetin (μmol·L^{-1})	**Parameters of contraction and relaxation kinetics of rat papillary muscle**			
	$T_{contr.}$ (msec)	$T_{1/2\ relax.}$ (msec)	$+dF/dt_{max}$ (mN/msec)	$-dF/dt_{max}$ (mN/msec)
Control	278.46	435.96	0.0084	0.0026
10	223.51	397.58	0.0097	0.0028
25	210.27	376.74	0.0104	0.0031
50	187.32	364.21	0.0109	0.0036
75	168.43	356.31*	0.0111*	0.0043
100	121.96*	321.02	0.0113*	0.0048*

Notes: $T_{contr.}$ – time from peak tension; $T_{1/2\ relax.}$ – time from to 50% relaxation; $+dF/dt_{max}$ – the maximum velocity of force development; $-dF/dt_{max}$ – the maximum velocity of relaxation; Parameters in control group were registered during the perfusion with physiological Krebs–Henseleit solution (pH = 7.4), and stimulation: 0.5 Hz with pulses of 5 V, and 5 msec (+36±0.5 °C). * – $p<0.05$ as compared to control group ($n = 5$).

It was observed from the experiments that 3',4'-dimethyl quercetin (100 μmol·L^{-1}) increased isometric contraction amplitude of the rat isolated papillary muscle from 2.345 mN up to 3.923 mN or 67.31% in comparison with the control. And also, at action this flavonoid (100 μmol·L^{-1}) decreased the duration of single isometric contraction for 34% in comparison with the control or from 1150 msec up to 764 msec (time from peak tension and to 50% relaxation, respectively). Thus, the parameter $+dF/dt_{max}$ increased to 34.1±3.2% in comparison with a group of the control with influence of that 3',4'-dimethyl quercetin (100 μmol·L^{-1}). Furthermore, the maximum velocity of relaxation $-dF/dt_{max}$ was considerable increased to 46.2±4.1% in comparison with a group of the control.

It is identified that the maximum velocity of force development ($+dF/dt_{max}$) and the maximum velocity of relaxation ($-dF/dt_{max}$) of the rat papillary muscles were significantly high in the experimental group than in the control group ($P < 0.05$).

Discussion

In many research studies, the cardiovascular effects of bioflavonoids were investigated. For example, in condition *in vitro*, it is shown that some flavonoids possess positive inotropic and lusitropic effects on isolated heart of experimental animals. Thus, authors of these works have supposed that these effects of flavonoids are connected with inhibition of phosphodiesterase (3'-5'-cAMP-phosphodiesterase) enzyme [14, 15].

It is shown that many of developed positive inotropic agents are phosphodiesterase inhibitors. The mechanism of the positive inotropic effect of phosphodiesterase inhibitors, an inhibition of the degradation of cAMP are explained with an increase in $[cAMP]_{in}$. This process leads to an increase in the I_{CaL} inward current during the AP, and leads to an increase in Ca^{2+} release from sarcoplasmic reticulum (SR), to an increase in the $[Ca^{2+}]_{in}$ and, therefore, to a positive inotropic effect [16].

Other investigations showed that flavonoids demonstrate a positive inotropic effect, through an increase in cAMP, which increases $[Ca^{2+}]_{in}$ [17–21].

It is known that, increasing concentration of $[cAMP]_{in}$ activates protein kinase A, which phosphorylates the L-type Ca^{2+}-channel, troponin I, and causes an increase of $[cAMP]_{in}$ and subsequently phosphorylation of contraction-controlling proteins, including $Ca^{2+}{}_{L}$-channels occured, and the amplitude force of contraction papillary muscles increased as well. Phosphorylation of these $Ca^{2+}{}_{L}$-channels promotes Ca^{2+} influx that triggers the release of Ca^{2+} from the RyRs of SR and $[Ca^{2+}]_{in}$ transient finally activates the contraction system of myocardium [22].

In some researches, only negative inotropic effects of flavonoids on contractility of cardiac muscles were shown. For example, it is identified that the fraction of flavonoids which extracted from plant *C. lyratiloba* decreases the amplitude force of rat papillary muscles [23].

And also, there are other impact mechanisms of flavonoids. For instance, at the department of Biophysics, National University of Uzbekistan (Tashkent, Uzbekistan), Umarova et al. (1998) it was investigated that flavonoids considerably inhibited the activity of the Na^{+},K^{+}-ATPase [24]. In addition to this Schüssler et al. (1995) determined that a positive inotropic effect of some flavonoids is connected with activation of adrenergic receptors in cardiomyocytes [14].

Thus, the obtained data in this research (Figure 4; 5) and the analysis of data from the different researches published on the basis of its results, it can be assumed that the positive inotropic effect of 3',4'-dimethyl quercetin happens to be based on cAMP-dependent mechanism (Figure 7).

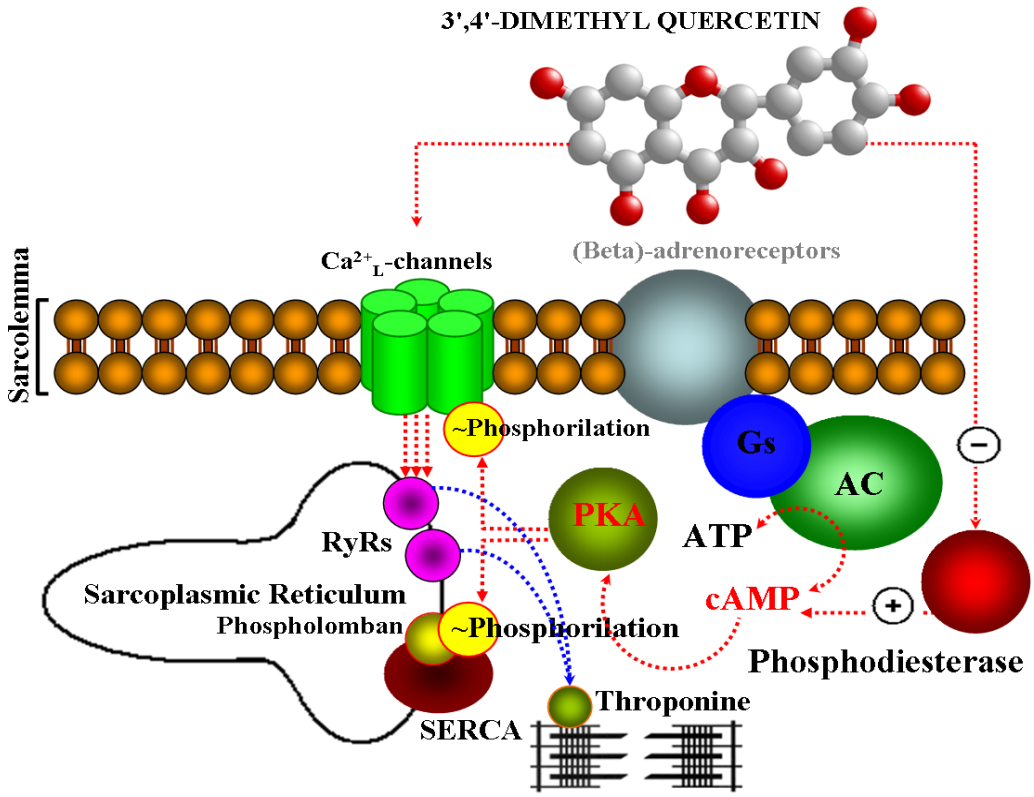

Figure 7. Hypothetical inpact mechanisms of inotropic effect of 3',4'-dimethyl quercetin on the rat myocardium. RyRs – Ryanodine Receptors or Sarcoplasmic reticulum Ca^{2+}–channels; SERCA – The Sarcoplasmic reticulum Ca^{2+}–ATPase; ATP – Adenosintriphosphat; G_s – Guanine nucleotide-binding proteins; AC – Adenylate cyclase; cAMP – Cyclic Adenosine 3',5'–monophosphate; PKA – proteine kinase A

In the experiment, it is shown that 3',4'-dimethyl quercetin dose-dependent (10–100 μmol·L^{-1}) increased in the maximum velocity of force development ($+dF/dt_{max}$), and the maximum velocity of relaxation ($-dF/dt_{max}$) of papillary muscles (*lusitropic effect*) (Table). This means that the contraction and relaxation kinetics are critical determinants of cardiac performance and currently the mechanism, regulation of myocardial contraction and relaxation kinetics are almost completely understood [25, 26].

According to Korotkich et al. (2006), an extract (the basic part consists from flavonoids) from plant *P. frutescens* (L) under *in vitro* condition shows positive inotropic and lusitropic effects on the rabbit myocardium. Also, the scientists supposed that such effects of *P. frutescens* (L.) extract can be connected with the increase of inward Ca^{2+} ions through $Ca^{2+}{}_L$-channels in the sarcolemmal and the increase of $[Ca^{2+}]_{SR}$. Moreover, the lusitropic effects of extract *P. frutescens* (L.) is explained with increase in $[cAMP]_{in}$ or inhibition of activity of phosphodiesterase enzyme. Through the rising process of concentration $[cAMP]_{in,}$ PKA activation occurs and $[Ca^{2+}]_{in}$ increases through the sarcolemmal $Ca^{2+}{}_L$-channels, "Ca^{2+} induced Ca^{2+} release" (CICR) from SR increases, and also at phosphorylation of phospholamban increases activation Ca^{2+}-ATPase of SR, parameter $-dF/dt_{max}$ increases as well [27].

Conclusion

In conclusion, the present study demonstrates that the positive inotropic effects of 3',4'-dimethyl quercetin in the rat papillary muscles can be mediated by increase in $[cAMP]_{in}$ which increase $[Ca^{2+}]_{in}$. And also, lusitropic effect of 3',4'-dimethyl quercetin increases in cAMP and inhibition of phosphodiesterase enzyme activates proteine kinase A, which phosphorylates regulator protein activity Ca^{2+}-ATPase – phospholamban and sarcoplasmic reticulum Ca^{2+}-channel (RyRs).

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Инотропное действие 3'4'-диметилкверцетина на сократительную активность папиллярной мышцы крысы

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Аннотация. Целью настоящего исследования явилось изучение инотропного действия 3'4'-диметилкверцетина на функциональную активность миокарда крыс. Регистрацию изометрической сила проводили с помощью механотрона (F30/Model D-79232; Hugo Sachs Elektronik, March-Hugstetten, Германия). Установлено, что 3'4'-диметилкверцетин (100 – 200 мкМ) вызывает положительный инотропный эффект. При этом, в присутствие блокатора потенциалзависимых $Ca^{2+}{}_L$-каналов (нифедипин) и блокатора β-адреноблокатора (пропранолол) положительный инотропный эффект 3'4'-диметил кверцетина почти полностью уменьшается. А также, 3'4'-диметилкверцетин дозозависимо увеличивает максимальную скорость развития силы и максимальную скорость расслабления папиллярной мыщцы.

Таким образом, полученные данные позволяют предположить, что положительный инотропный эффект 3'4'-диметилкверцетина может быть связан с активацией β-адренорецепторов, при этом увеличивается концентрация цАМФ и следовательно увеличивается $[Ca^{2+}]_{in}$ в кардиомиоцитах. А также, луситропный эффект 3'4'-диметилкверцетина может быть связан с увеличением цАМФ; блокированием фермента фосфодиэстеразы; активацией протеинкиназы А и фосфорилированием регуляторного белка Ca^{2+}-АТФазы – фосфоламбана и фосфорилированием RyR.

Ключевые слова: папиллярная мышца, 3',4'-диметил кверцетин.