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Research Article

Cardioprotective Effect of -(4'-Methoxyphenyl)-6,7-Dimethoxy-1,2,3,4-Tetrahydroisoquinoline

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Abstract

In studies, 1-(4'-methoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (F-4) and 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (F-36) cardioprotective properties of alkaloids were studied. In this case, cardiomyocyte Ca2+-transport systems in the presence of their specific inhibitors were carried out under hypoxia conditions. Blockers of potential-dependent Ca2+-channels, such as nifedipine and Na+/Ca2+- exchange blockers such as NiCl2 were used. The purpose of this study is to evaluate the cardioprotective properties of F-4 and F-36 isoquinoline alkaloids under hypoxia conditions in vitro and to expand the understanding of hypoxia-related molecular signaling pathways.

Keywords: *Papillary Muscle; Ca-Channels; Na+/Ca2+- Exchange; Hypoxia*

Introduction

Today, cardiovascular diseases are one of the main causes of death in developed countries [1]. According to the World Health Organization, 17.5 million people die each year from various heart diseases [2]. The modern concept of prevention and treatment of these diseases and the identification of biologically active substances isolated from medicinal plants with cardioprotective properties are one of the urgent problems of today [3]. Among them, it is important to find new drugs with cardioprotective properties, with high efficiency and few side effects and to determine their mechanisms of action. Among the heterocyclic compounds, alkaloids have a wide range of pharmacological activities, and many of them have been used in traditional or modern medicine or as starting points for drugs [4]. Today, the most studied alkaloids from a pharmacological point of view are isoquinoline, indole and purine alkaloids. Also, from the isoquinoline alkaloids, the pharmacology of berberine and its clinical use for its antiarrhythmic effects have also begun to be used in the treatment of hypertension [5]. In general, drugs whose component consists mainly of isoquinoline alkaloids are effectively used today in the treatment of atherosclerosis, hypertension, myocardial infarction, cardiomyopathy, heart failure and arrhythmias [6]. Taking this into account, the cardioprotective properties of F-4 and F-36 isoquinoline alkaloids were studied.

Materials and Methods

Purebred, white rats (100 - 250g) were used in the experiments, and the international Declaration of Helsinki and the International Council of Medical Scientific Societies (CIOMS) (1985) rules for working with experimental animals were followed.

The mechanographic method (Mayflower Tissue Bath System, Hugo Sachs Electronic, Germany) and the hardware-software complex (LabScibe 2, World Precision Instruments, USA) were used to study the mechanism of action of biologically active substances on the functional activity of the myocardium of experimental animals *in vitro*. Oxygenated carbogen (O_2 - 95% and CO_2 - 5%) with the following

composition is continuously perfused with Krebs saline: NaCl - 150; KCl - 4; $CaCl_2$ - 1,8; $MgCl_2$ - 1; $NaHCO_3$ - 14; NaH_2PO_4 - 1,8; $C_6H_{12}O_6$ - 11,5; 11 $C_6H_{12}O_6$ (pH = 7,4). A hypoxia model was called by substituting nitrogen (N - 95% and O_2 - 5%) for oxygen in the perfused Krebs saline solution described above.

Data are expressed as mean ± SD. Control values between groups were compared by analysis of variance. The Student's t-test was used to compare two means. A probability of less than 0.05 was taken as a statistically significant difference. Statistical analysis was performed using OriginPro 7.5 software (OriginLab Co., U.S.A).

Results and Discussion

In preliminary studies, it was found that F-4 and F-36 isoquinoline alkaloids have a positive inotropic effect on the activity of papillary muscle contraction of the rat heart and increase the force of muscle contraction at all concentrations. In the experiments, it was noted that F-4 (10-100 μM) and F-36 (10-120 μM) alkaloids increase the force of cardiac papillary muscle contraction by 32.9 ± 4.6% and 75.7 ± 4.7% compared to the control (Figure 1).

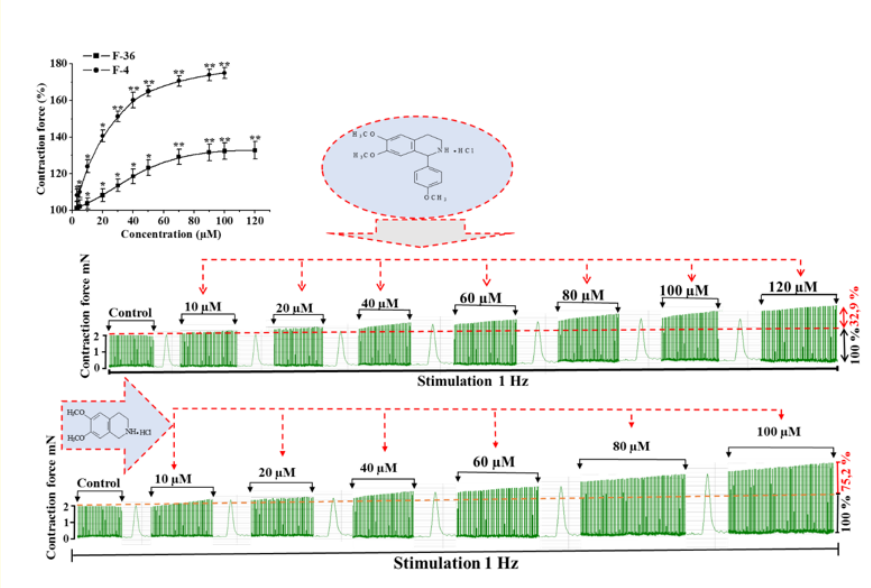

Figure 1: *Dose-dependent effects of F-4 and F-36 isoquinoline alkaloids on the contractile activity of rat heart papillary muscle. The ordinate axis shows the amplitude value of the contraction force expressed as a percentage (%) compared to the maximum. The frequency of stimulation of the drug is 1 Hz. In all cases *- p < 0.05; **- p < 0.01 n = 6.*

There are a large number of pathophysiological processes underlying the development of heart diseases, among which the dysfunction of Ca^{2+} homeostasis and Ca^{2+}-transport systems of cardiac muscle cells plays a leading role. Ischemia/hypoxia conditions play a key role in the development of these disorders, and the main energy source in cardiomyocytes is ATP and creatine phosphate products [7]. At the same time, in the conditions of ATP and creatine phosphate deficiency, the function of the Ca^{2+}-transport system, which is directly related to the energy consumption activity of macroergs, is disturbed. These disorders, in turn, negatively affect the functions of other Ca^{2+}-transport systems involved in maintaining Ca^{2+} homeostasis and circulation of Ca^{2+} ions in cardiac muscle cells [8].

Taking into account the above, the hypoxia model was called by replacing 95% oxygen in the incubation medium with 95% nitrogen in the next experiments. It was found that when the perfused Krebs solution is aerated with nitrogen for 60 minutes, the force of papillary muscle contraction is reduced to 27.6 ± 3.1% compared to the control (Figure 2A and 2B).

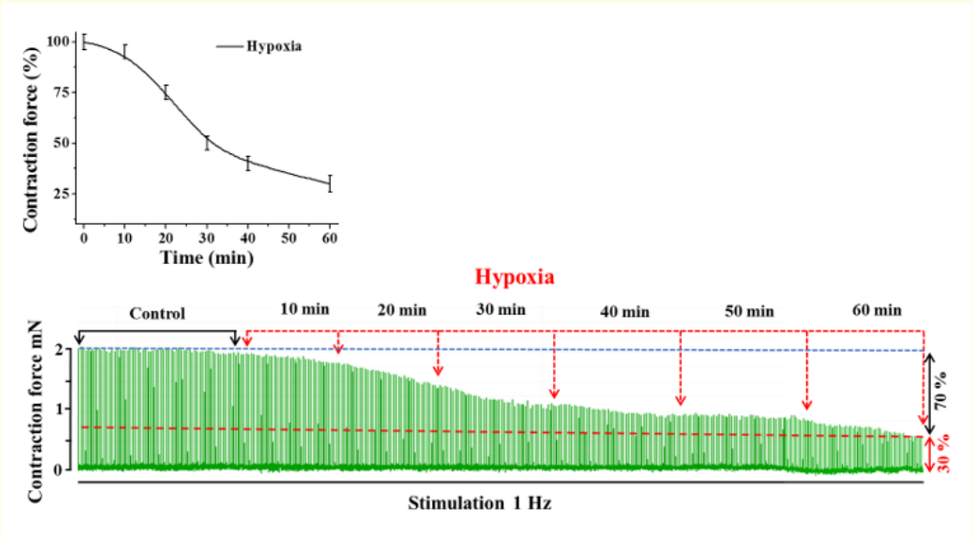

Figure 2: *Effect of hypoxia on the contractile activity of the papillary muscle of the rat heart. On the ordinate axis - muscle contraction force, the control obtained under normal oxygenation of physiological solution is expressed as a percentage and taken as 100%. On the abscissa axis is the deoxygenation time of the solution perfused with nitrogen. The frequency of stimulation of the drug is 1 Hz. In all cases *- p < 0.05; **- p < 0.01 n = 5. B. Papillary muscle contractile activity under hypoxia (original entry).*

Considering that the force of papillary muscle contraction is carried out with the participation of Ca^{2+} ions, the results of these experiments show that the decrease in muscle contraction force under hypoxia is accompanied by a decrease in $[Ca^{2+}]_i$ ions [9].

In order to evaluate the cardioprotective properties of isoquinoline alkaloids mentioned above, the effect of hypoxia on the papillary muscle contraction activity of the rat heart was studied. The effect of F-4 (100 μM) and F-36 (120 μM) isoquinoline alkaloids under hypoxia was 72.6 ± 5.1% and 79.9 ± 4.9%, respectively, compared to the control (Figure 3).

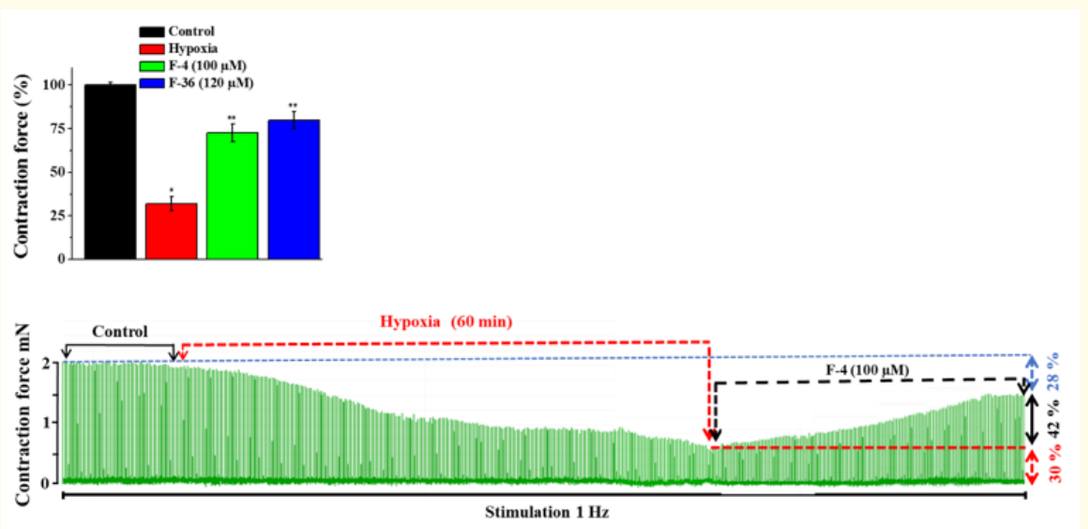

Figure 3: *Effects of isoquinoline alkaloids F-4 and F-36 under hypoxic conditions on the contractile activity of the papillary muscle of the rat heart. On the ordinate axis, the amplitude value of the contraction force is expressed as a percentage (%) compared to the maximum. The frequency of stimulation of the drug is 1 Hz. In all cases *- p < 0.05, **- p < 0.01; n = 4.*

The obtained data show that the studied alkaloids have cardioprotective properties under hypoxia conditions *in vitro* and effectively eliminate the disturbances in the contraction activity of papillary muscle cells caused by hypoxia. One of the main causes of positive inotropism is the modulation of Ca^{2+}_{L}-channel activity in cardiomyocytes and, in turn, changes in $[Ca^{2+}]_i$ [10]. In subsequent experiments, the positive inotropic effect of the studied substances was studied using nifedipine, a specific blocker of the potential-dependent activating Ca^{2+}_{L}-channel located in the cardiomyocyte sarcolemma under hypoxia. It was observed that nifedipine (IC_{50} = 0.01 μM) decreased papillary muscle contraction force by 17.8 ± 4.1% compared to control in hypoxia induced *in vitro*. In this case, the effect of F-4 (100 μM) and F-36 (120 μM) isoquinoline alkaloids on papillary muscle contraction force was 42.4 ± 5.1% and 49.9 ± 4.9%, respectively, compared to the control (Figure 4). It can be seen that the isoquinoline alkaloids F-4 and F-36 indicate the presence of Ca^{2+}_{L}-channels in the cardioprotective properties under hypoxia conditions.

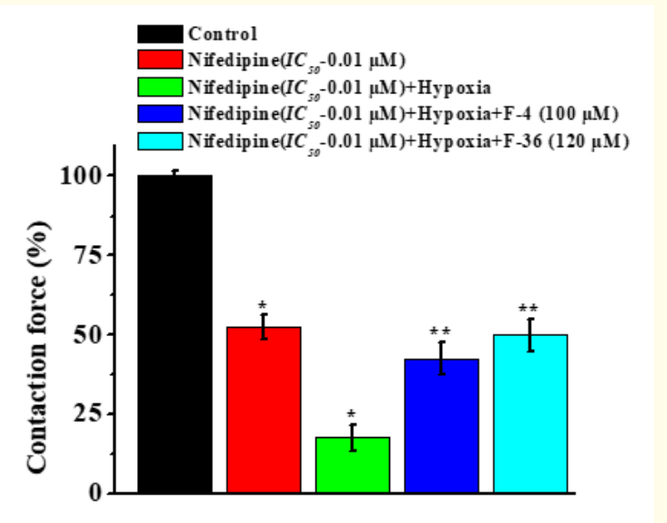

Figure 4: *Evaluation of the participation of Ca2+L-channels in the hypoxia of F-4 and F-36 isoquinoline alkaloids on the activity of papillary muscle contraction of the rat heart. The ordinate axis shows the amplitude value of the contraction force expressed as a percentage (%) compared to the maximum. The frequency of stimulation of the drug is 1 Hz. In all cases *- p < 0.05, **- p < 0.01; n = 5.*

It is known that the Na^+/Ca^{2+}-exchange system in cardiomyocytes in normal physiological condition is the main system that brings Na^+ ions into the cell [11] and releases Ca^{2+} ions out of the cell. Therefore, in the experiments, we studied the effect of the studied substances on the cardiomyocyte Na^+/Ca^{2+}-exchange system under hypoxia conditions [12]. In order to evaluate the effect of isoquinoline alkaloids F-4 (100 μM) and F-36 (120 μM) on papillary muscle contraction activity, the location of the Na^+/Ca^{2+}-exchange system located in the sarcolemma of cardiomyocytes was used at a concentration of 10 mM of its non-specific blocker - $NiCl_2$. Under these conditions, papillary muscle contraction force was 37.8 ± 4.1% and 63.9 ± 4.9%, respectively, compared to the control (Figure 5).

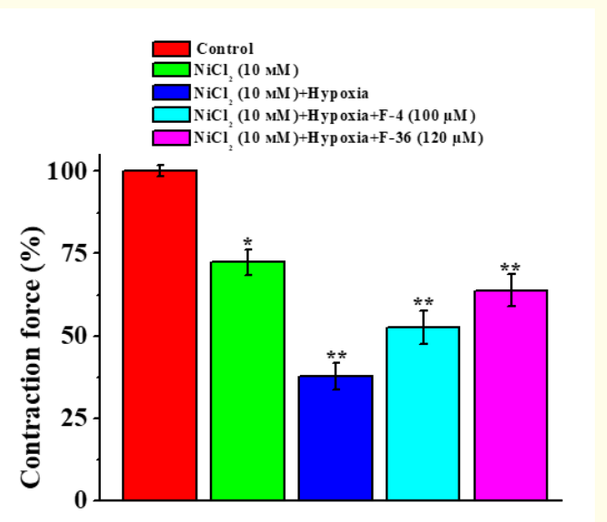

Figure 5: *Evaluation of role of Na+/Ca2+-exchange system of F-4 and F-36 isoquinoline alkaloids on papillary muscle contractile activity of rat heart under hypoxia. The ordinate axis shows the amplitude value of the contraction force expressed as a percentage (%) compared to the maximum. The frequency of stimulation of the drug is 1 Hz. In all cases *- p < 0.05, **- p < 0.01; n = 5.*

Experiments conducted with $NiCl_2$ under hypoxia revealed that the positive inotropic and cardioprotective activity of the studied isoquinoline alkaloids indicates that the Na^+/Ca^{2+}-exchange system is less involved.

In general, based on the results of the above research, we can conclude that F-4 and F-36 isoquinoline alkaloids have strong cardioprotective properties, and it was found that they effectively eliminate disturbances in the activity of muscle contraction in hypoxia induced in the papillary muscle preparation of the rat heart under *in vitro* conditions.

Conclusion

It can be concluded that this effect of alkaloids goes partly through Na^+/Ca^{2+}-exchange and mainly through modulation of Ca^{2+}_L- channels.

Acknowledgements

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Conflict of Interest

The authors have declared that no conflict of interest exists.

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