ISSN 2231-2218

ASIAN JOURNAL OF PHARMACEUTICAL AND BIOLOGICAL RESEARCH

AJPBR

Indexed by:

ROAD Crossref Universal Impact Factor IMPACT FACTOR SEARCH

Asian journal of Pharmaceutical and biological research 2231-2218
http://www.ajpbr.org/
Universal IMPACT factor 7
SJIF 2022: 4.465
Volume 12 Issue 3
SEP-DEC. 2023

Asian journal of Pharmaceutical and biological research 2231-2218
http://www.ajpbr.org/
Universal IMPACT factor 7
SJIF 2022: 4.465
Volume 12 Issue 3
SEP-DEC. 2023

Effects of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride alkaloid on cardiomyocyte Na^+/Ca^{2+} exchange under normoxia and hypoxia conditions

[1*]Sadriddin N. Boboev, [1]Inoyat Z. Zhumaev, [1]Pulat B. Usmanov, [1]Rustamov Sh. Yusubovich, and [2]Sherzod N. Zhuraqulov

[1]Institute of Biophysics and Biochemistry at NUUz

[2]Institute of Chemistry of Plant Substances of the AS RUz

sadriddin-2022@mail.ru

Abstract: The purpose of this study is to evaluate the role of Na^+/Ca^{2+}-exchange in the cardioprotective properties of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (F-36) alkaloid. The alkaloid F-36 (from 5 μM to 100 μM) was found to have a positive inotropic effect on the contractile activity of the papillary muscle of the rat heart [1]. Positive inotropic effect of F-36 alkaloid was found to affect cardiomyocyte Na^+/Ca^{2+}-exchange and this was confirmed in experiments with $NiCl_2$ and ouabain.

Keywords: papillary muscle, Na^+/Ca^{2+}-exchange, Na^+/K^+-ATPase, isoquinoline alkaloid.

INTRODUCTION. Treatment and prevention of diseases of the cardiovascular system are one of the most important tasks of today. Morphine, codeine, caffeine, strychnine, berberine, atropine, galantamine, cytisine, etc. are biologically active substances extracted from medicinal plants and are used in modern medicine and pharmacology to treat various diseases [2,3]. The most studied alkaloids are indole and isoquinoline alkaloids .

Also, 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. Taking this into account, the [4] effect of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (F-36) alkaloid on Na^+/Ca^{2+} exchange in rat heart papillary muscle cells under normoxia/hypoxia conditions was studied.

It is known that the Na^+/Ca^{2+} exchange system [5] is physiologically important in cardiac muscle contraction-relaxation. During membrane depolarization, the Na^+/Ca^{2+} exchange system is important in the release of Ca^{2+} from the SR, as well as L-type Ca^{2+} channels in the plasmalemma [6]. Modulation of the function of Na^+/Ca^{2+} exchange is considered important in the origin of some diseases of the cardiovascular system [7].

Its non-specific inhibitor $NiCl_2$ and ouabain were used to investigate the effect of isoquinoline alkaloid F-36 on myocardial cell Na^+/Ca^{2+} exchange. Ouabain is a cardiac glycoside that acts by inhibiting Na^+/K^+–ATPase and sodium-potassium ion channels (but it is not selective) [8]. As a result of inhibition of Na^+/K^+–ATPase [9], ouabain causes Na^+/Ca^{2+} exchange to work in reverse mode. This leads to increased cardiac contraction and increased cardiac vagal tone. Changes in ionic gradients caused by ouabain can also affect cell membrane tension and cause cardiac arrhythmias.

Rat heart papillary muscle preparations were used to study the effect of isoquinoline alkaloid F-36 on Na^+/Ca^{2+} exchange in myocardial cells.

Papillary muscle preparations are a convenient object for studying the role of the intracellular signal system and various types of ion channels in maintaining the electrical and contractile activity of the heart muscle, as well as for explaining the methods of their pharmacological regulation.

MATERIAL AND METHODS

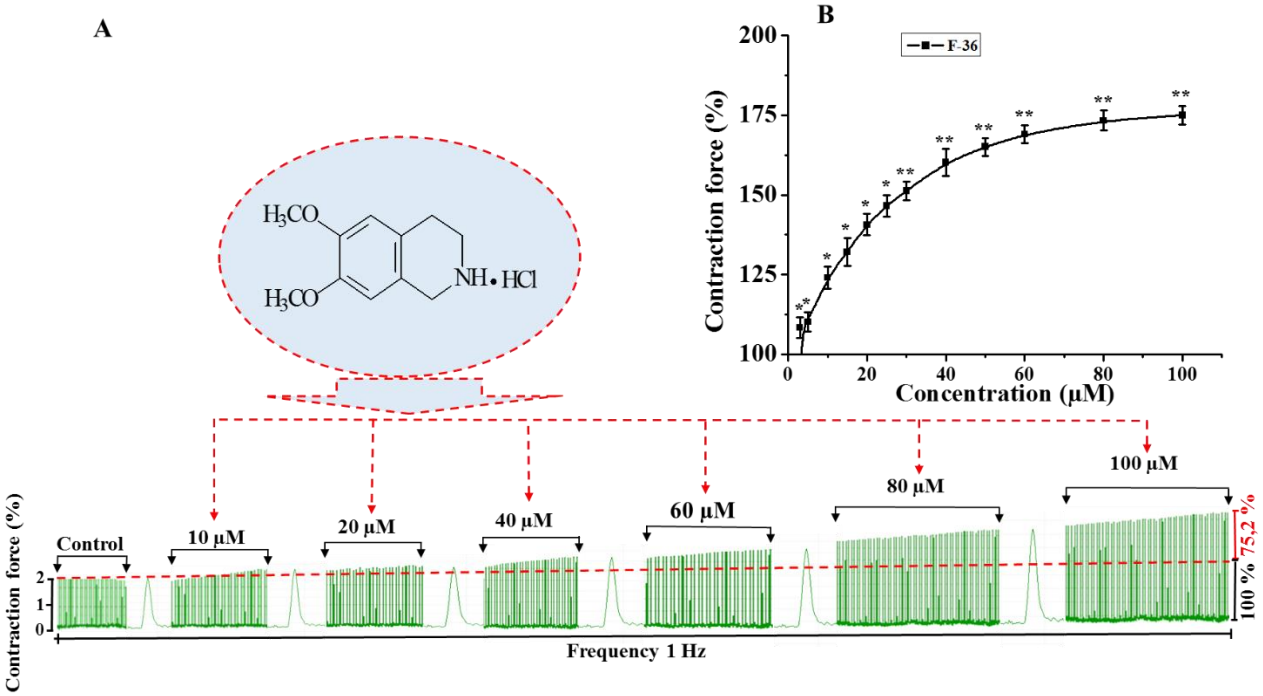
Purebred, white rats (200-250 gr.) were used in the experiments. The international Declaration of Helsinki and the rules developed by the Council of International Medical Scientific Societies (CIOMS) (1985) were followed in the handling of experimental animals. The experimental animals were anesthetized with diethyl ether, the chest cavity was opened surgically, the heart was removed, and a papillary muscle preparation was prepared in a petri dish with Krebs-Henseleit saline solution, and a mechanographic device (Mayflower Tissue Bath System, Hugo Sachs

Asian journal of Pharmaceutical and biological research 2231-2218
http://www.ajpbr.org/
Universal IMPACT factor 7
SJIF 2022: 4.465
Volume 12 Issue 3
SEP-DEC. 2023

Electronic,) was used to record the contraction activity of the papillary muscle preparation. Germany) and a hardware-software complex (LabScibe 2, World Precision Instruments, USA) was used. The papillary muscle isolated from the left ventricle of the rat heart was [10] placed in a 20 ml chamber, and continuously perfused with Krebs' physiological solution of oxygenated carbogen (O_2–95% and CO_2–5%) with the following composition: 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 mM; (pH=7.4) [11].

RESULTS AND DISCUSSION

In the course of the research, it was found that F-36 isoquinoline alkaloid has a positive inotropic effect on the activity of papillary muscle contraction of the rat heart and significantly increases the force of muscle contraction [1]. When examining the dose-dependent effect of isoquinoline alkaloid F-36 on the activity of papillary muscle contraction, it was noted that it showed a positive inotropic effect starting from 5 μM, and at 100 μM, it increased the force of muscle contraction by [12] 75.7±4.7% [13] compared to the control (control was taken as 100%). was done (Fig.1 A, B).



Asian journal of Pharmaceutical and biological research 2231-2218
http://www.ajpbr.org/
Universal IMPACT factor 7
SJIF 2022: 4.465
Volume 12 Issue 3
SEP-DEC. 2023

Fig. 1. Effect of F-36 alkaloid on the contractile activity of the papillary muscle of the rat heart. **A.** Increasing the force of contraction of the papillary muscle of the alkaloid F-36 (original recording). **B.** Dose-dependent increase in the force of contraction of the papillary muscle of the alkaloid F-36. The y-axis shows the force of contraction of the papillary muscle, expressed as a percentage of the control, taken as 100%, and the abscissa shows the alkaloid concentration (μM), (*-p<0.05; **-p<0.01). Stimulation frequency 1 Hz (t=+36±0.5°C; n=5).

Alteration of Na^+/Ca^{2+}-exchange function in heart muscle cells leads to disturbance of Ca^{2+}-homeostasis, and restoration of $[Ca_{2+}]_i$ to initial level in heart and smooth muscle cells is ensured by SERCA2 [14,15,16]. Taking into account the above, in the next experiments, experiments were conducted on the function of cardiomyocyte Na^+/Ca^{2+}-exchange in the presence of its non-specific blocker $NiCl_2$ (10 mM).

It was found that $NiCl_2$ (10 mM) reduced papillary muscle contraction force to 73.4±3.4% compared to the control. Under these conditions, the effect of the alkaloid F-36 (100 μM) on papillary muscle contraction [17] activity was 93.1±3.9%, respectively, compared to the control [18] (Fig.2).

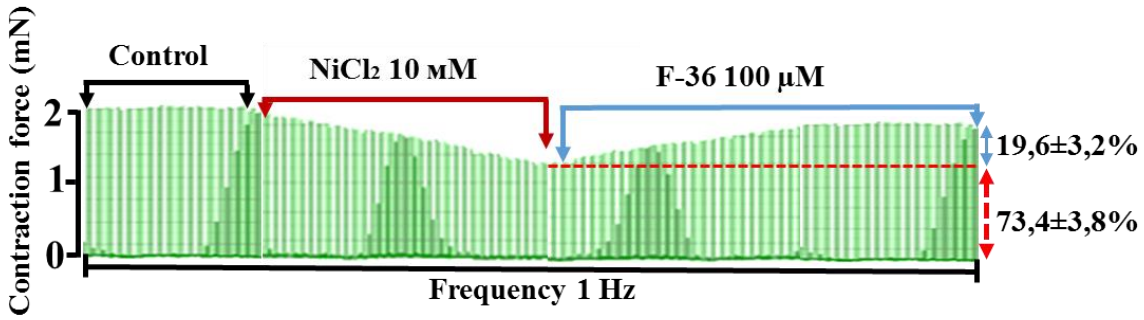


Fig. 2. Effects of F-36 on papillary muscle contraction force in the presence of $NiCl_2$. On the ordinate axis - the amplitude value of the contraction force is expressed as a percentage (%) compared to the maximum. n=5.

Based on the above experiments, it can be concluded that the positive inotropic effect of the F-36 alkaloid indicates the participation of Na^+/Ca^{2+} exchange. To further prove the results of this study, experiments were conducted with the presence of ouabain.

Asian journal of Pharmaceutical and biological research 2231-2218
http://www.ajpbr.org/
Universal IMPACT factor 7
SJIF 2022: 4.465
Volume 12 Issue 3
SEP-DEC. 2023

By inhibiting Na^+/K^+-ATPase, ouabain causes an increase in Na^+ [19] content in cardiomyocytes, and as a result, an increase in papillary muscle contraction force is observed due to increased entry of Ca^{2+} ions into the cell through Na^+/Ca^{2+}-exchange [20,21,22]. When we examined the effect of ouabain on papillary muscle contractile activity, it showed a positive inotropic effect in a dose-dependent manner, increasing the force of contraction by 76.1±4.4% compared to the control (100% obtained) at a concentration of 20 μM. When the effect of ouabain alkaloid F-36 on papillary muscle contractile activity was examined under present conditions, it was observed that it increased muscle contraction force by 112.2±4.5% at a concentration of 100 μM (Fig. 3).

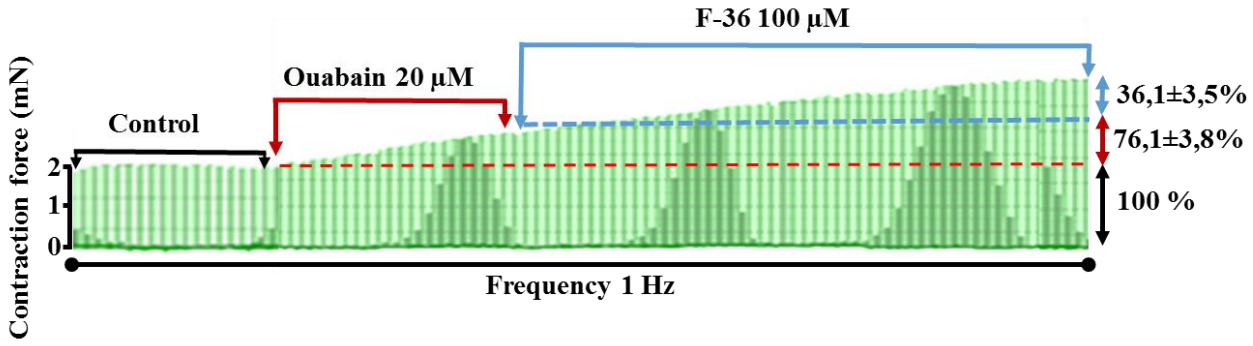


Fig. 3. Effects of F-36 on papillary muscle contraction force in the presence of ouabain. On the ordinate axis - the amplitude value of the contraction force is expressed as a percentage (%) compared to the maximum. *-p<0.05 in all cases; n=5.

The analysis of the results of these experiments shows that the studies conducted with the participation of ouabain completely prove the results of the experiments conducted with $NiCl_2$.

It is known that the Na^+/Ca^{2+}-exchange system in cardiomyocytes in a normal physiological state is the main system that brings Na^+ ions into the cell and releases Ca^{2+} ions out of the cell. Therefore, in the experiments, we investigated the effect of F-36 alkaloid on the cardiomyocyte Na^+/Ca^{2+}-exchange system under hypoxia. To evaluate the effect of F-36 alkaloid (100 μM) on papillary muscle contraction activity, the role of the cardiomyocyte Na^+/Ca^{2+}-exchange system was used at a concentration of 10 mM of its blocker $NiCl_2$. In the presence of $NiCl_2$, the strength of

Asian journal of Pharmaceutical and biological research 2231-2218
http://www.ajpbr.org/
Universal IMPACT factor 7
SJIF 2022: 4.465
Volume 12 Issue 3
SEP-DEC. 2023
papillary muscle contraction in hypoxia was 34.1±4.1% compared to the control. Under these conditions, it was found that F-36 alkaloid (100 μM) increases muscle contraction force by 52.5±4.1% (Fig. 4).

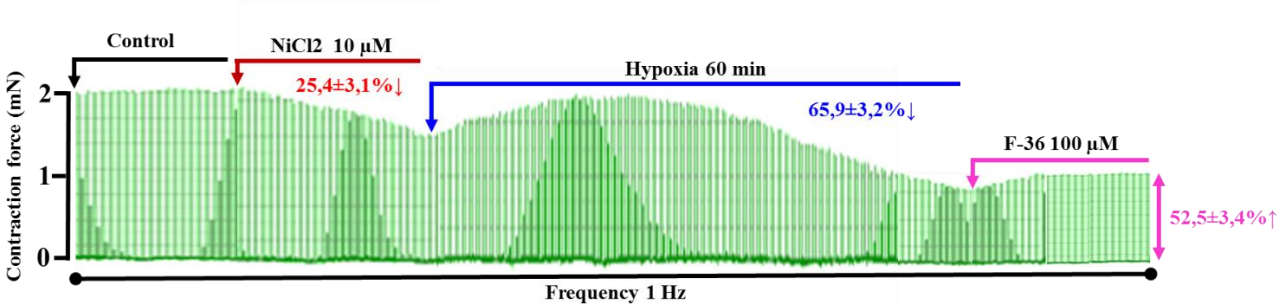


Fig. 4 Evaluation of the role of Na^+/Ca^{2+}-exchange system of F-36 alkaloid under hypoxia. On the ordinate axis - the amplitude value of the contraction force is expressed as a percentage (%) compared to the maximum. The frequency of stimulation of the drug is 1 Hz. In all cases * - $p<0.05$; n=5.

The results of this study indicate that the F-36 alkaloid is involved in Na^+/Ca^{2+} exchange in the effective reduction of the contraction activity of the papillary muscle of the rat heart under hypoxia conditions in vitro.

Conclusion

Na^+/Ca^{2+} exchange has been found to be important in changes in muscle contraction caused by hypoxia-induced myocardial injury [23]. Based on the results of the above research, we can say that F-36 alkaloid has a positive inotropic effect and cardioprotective properties by modulating the function of Na^+/Ca^{2+} exchange. This assumption was confirmed in experiments with $NiCl_2$ and ouabain.

Acknowledgments. This work was supported by a grant F-OT-2021-154 from the Coordinating Committee for Development of Science and Technology under the Cabinet of Ministers of the Republic of Uzbekistan.

Conflict of interest

The authors have declared that no conflict of interest exists.

References

1. Priyanka Mishra, Vinit Raj, Archana S Bhadauria, Ashok K Singh, Amit Rai, Pranesh Kumar, Amit K Keshari, Arnab De, Amalesh Samanta, Umesh Kumar, Dinesh Kumar, Biswanath Maity, Sneha Nath, Anand Prakash, Kausar M Ansari, Sudipta Saha // 6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid attenuates colon carcinogenesis via blockade of IL-6 mediated signals// Biomed Pharmacother// 2018; P: 282-295

2. Michael Heinrich, Jeffrey Mah, and Vafa Amirkia. Alkaloids Used as Medicines: Structural Phytochemistry Meets Biodiversity-An Update and Forward Look // Molecules. 2021 Apr; 26(7): 1836.

3. Joanna Kurek. Alkaloids - Their Importance in Nature and Human Life // November 13th, 2019

4. Zhi-Xing Qinga, Peng Yang , Qi Tang , Pi Cheng , Xiu-Bin Liu , Ya-jie Zhenga , Yi-Song Liu and Jian-Guo Zeng// Isoquinoline Alkaloids and their antiviral, antibacterial, and antifungal activities and structure-activity relationship// Current Organic Chemistry 2017 V 21 P: 1-15

5. Cargnelli, Gabriella, Sergio Bova, and Sisto Luciani. "Effects of amiloride in guinea-pig and rat left atrial contraction as affected by frequency of stimulation and $[Ca^{2+}]_0$-$[Na^{+}]_0$ ratio: role of Na^{+}/Ca^{2+}exchange", British Journal of Pharmacology, 1989 P: 533-541

6. Daniela Marasco, Caterina Vicidomini, Pawel Krupa, Federica Cioffi, Pham Dinh Quoc Huy, Mai Suan Li, Daniele Florio, Kerensa Broersen, Maria Francesca De Pandis, Giovanni N Roviello. Plant isoquinoline alkaloids as potential neurodrugs: A comparative study of the effects of benzo[c]phenanthridine and berberine-based compounds on β-amyloid aggregation // Chem Biol Interact, 2021 Jan 25;334:109300.

7. Sham JSK, Hatem SN, Morad M. Species differences in the activity of the Na^{+}-Ca^{2+} exchanger in mammalian cardiac myocytes. J Physiol. 1995;*488*: 623–631..

8. Dobler, Susanne; Dalla, Safaa; Wagschal, Vera; Agrawal, Anurag A. (2012-08-07). "Community-wide convergent evolution in insect adaptation to toxic cardenolides by substitutions in the Na, K-ATPase". Proceedings of the National Academy of Sciences. 109 (32): 13040–13045.

9. M. A. MATLIB. "Role of Sarcolemmal Membrane Sodium-Calcium Exchange inVascular Smooth Muscle Tension", Annals of the New York Academy of Sciences, 12/1991

10. A.-B. Jeppsson. "Steric Aspects of Agonism and Antagonism at β-Adrenoceptors: Experiments with the Enantiomers of Terbutaline and Pindolol", Acta Pharmacologica et Toxicologica, 03/13/2009

11. D Lacroix. "Repolarization abnormalities and their arrhythmogenic consequences in porcine tachycardia-induced cardiomyopathy", Cardiovascular Research, 04/2002

12. Inoyat Z. Zhumaev, Sadriddin N. Boboev, Pulat B.Usmanov, Shakhnoza B. Qurbonova et al. "Mechanism of Positive Inotropic Effect of Vincanine on Cardiac Muscle Contraction Activity", Biomedical and Pharmacology Journal, 2022

13. Sadriddin N. Boboev, Inoyat Z. Jumayev, Pulat B. Usmanov, Sherzod N. Zhurakulov.// Description of cardioprotective properties of some isoquinoline alkaloids// Journal of Heart and Vasculature. 2022 P: 1-5

14. Yu SP, Choi DW (1997). "Na^+-$Ca2^+$ exchange currents in cortical neurons: concomitant forward and reverse operation and effect of glutamate". The European Journal of Neuroscience. 9(6): 1273–81. 1997.1482.x

15. Liu, Y., Ning, Z., Chen, Y. et al. Aerodynamic analysis of SARS-CoV-2 in two Wuhan hospitals. Nature 582, 557–560 (2020).

16. Pulat B. Usmanov1, Inoyat Z. Jumayev, Shavkat Yu. Rustamov, Abdisalim A. Zaripov, Adilbay T. Esimbetov, Sherzod N. Zhurakulov and Valentina I. Vinogradova. The Combined Inotropic and Vasorelaxant Effect of DHQ-11, a Conjugate of Flavonoid Dihydroquercetin with Isoquinoline Alkaloid 1-aryl-6,7-dimethoxy-1,2.3,4-tetrahydroisoquinoline // Biomedical & Pharmacology Journal, June 2021. Vol. 14(2), p. 651-661

17. A M Rose, R Valdes Jr // Understanding the sodium pump and its relevance to disease// Clin Chem. 1994 Sep;40(9):1674-85.

18. Lijun L., Jian W. and David J.K. Regulation of Cardiac Remodeling by Cardiac Na^+/K^+-ATPase Isoforms // Front. Physiol. – 2016. – V.7. – P. 1-9.

19. Sh. S. Khushmatov, I. Z. Zhumaev, Sh. N. Zhurakulov, A. Sh. Saidov, and V. I. Vinogradova. Synthesis and Comparative Inotropic Effects of Several Isoquinoline Alkaloids // Pharmaceutical Chemistry Journal Vol. 54, No. 1, pp. 9 – 13, January 2020.

20. Inoyat Jumayev, Pulat Usmanov, Shavkat Rustamov1 and Sherzod Zhurakulov. Comparative Inotropic Effects of the Some Isoquinoline Alkaloids // Biomedical & Pharmacology Journal, March 2020. Vol. 13(1), p. 325-333

21. B. N. Eigel, H. Gursahani, and R. W. Hadley. Na^+/Ca^{2+} exchanger plays a key role in inducing apoptosis after hypoxia in cultured guinea pig ventricular myocytes // Am J Physiol Heart Circ Physiol287: H1466 –H1475, 2004.