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Review Article

Description of the Mechanism of Positive Inotropic Action of the Isoquinoline Alkaloid F-18

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Abstract

This study evaluated the mechanism of inotropic effect of an isoquinoline alkaloid derivative, 1-(2′-bromine-4′,5′-dimethoxyphenyl)-6,7-dimethoxy-1,2,3,4- tetrahydroisoquinoline (F-18) using electrically stimulated rat left ventricular papillary muscle of rat. The F-18 alkaloid have been shown to have positive inotropic effect on papillary muscle contraction activity, IC_{50} value -14,6 μM. Ca^{2+}L-channel blocker - nifedipine was used in experiments. Inotropic effects of F-18 isoquinoline alkaloid on cardiomyocytes were suggested, based on results obtained in experiments carried in cardiomyocytes SR Ca^{2+}- transport systems modulation.

Keywords: Papillary muscle; Inotropic effect; Isoquinoline alkaloid

Introduction

Isoquinoline alkaloids constitute one of the largest groups of plant-derived compounds with a wide range of pharmacological activities are a promising candidate for developing new cardiovascular drugs. A significant number of isoquinoline alkaloids possess a potent antiarrhythmic activity mediated through multiple cellular mechanisms [1]. The antiarrhythmic effect of the well-known representative of these alkaloids tetrandrine are provided by blockage of L- and T-types calcium and sodium channels with slow recovery kinetics, thus terminating acute episodes of paroxysmal supraventricular tachycardia [2]. It also has been demonstrated that tetrandrine exerted a substantial positive inotropic and chronotropic effects associated with decreased intracellular Ca^{2+} due to the blockage of the voltage-operated Ca^{2+} channels and modulation of the sarcoplasmic reticulum Ca^{2+} loading and release functions [3]. Positive inotropic of tetrandrine, like most antiarrhythmic drugs, resulting in reductions in cardiac contractility and cardiac output is a serious adverse effect, limit its use in patients with already impaired left ventricular function [4].

Recently, with the aim to find new effective antiarrhythmic agents a series of hydroxyethyl derivatives of 1-aryltetraisoquinoline alkaloids were synthesized [5, 6]. In previous studies the effects of these derivatives on rat left ventricular papillary muscle contractility we found that among them the most potent positive inotropic activity exert 1-(2′-bromine-4′,5′-dimethoxyphenyl)-6,7-dimethoxy-1,2,3,4- tetrahydroisoquinoline, designated as F-18. Therefore, the aim of this study was further to characterize the positive inotropic effect of this new isoquinoline derivative and to define the mechanism of this action (Figure 1). The chemical structure of the synthesized 1-(2′-bromine-4′,5′-dimethoxyphenyl)-6,7-dimethoxy-1,2,3,4- tetrahydroisoquinoline is proven with the

help of NMR data ^{1}N and ^{13}C spectra. In NMR ^{1}N, the spectrum of the protons of the aromatic ring N-5 and N-8 is observed in the form of singlets at 6.64 ppm. VA δ 6.26 ppm, the n-1 of the methyine group resonates in the form of a singlet at δ 5.43 ppm. Signals NMR ^{1}N and ^{13}C confirmed education 1-(2′-bromine-4′,5′-dimethoxyphenyl)-6,7-dimethoxy-1,2,3,4- tetrahydroisoquinoline (4a) $C_{19}H_{22}O_4NBr$.

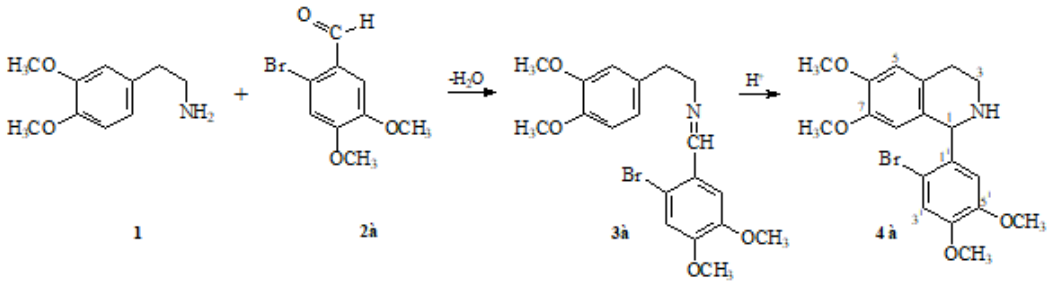

Figure 1: Chemical structure of Isoquinoline alkaloid.

Material and Method

All experimental protocol and conditions for preoperative care were approved by the animal use committee of the Institute of Biophysics and Biochemistry. Adult male Wistar rats weighing 200–250g were anesthetized with sodium pentobarbital (50 mg/kg^{-1}, i.p.) and then sacrificed by cervical dislocation. The papillary muscles from the left ventricles of the rat hearts about 0,5-0,8 mm in diameter and 1-3 mm in length were dissected and mounted in a tissue bath (STEIRT, HSE, Germany) of 3 ml volume and superfused at a rate of 20 ml min^{-1} with Krebs solution. The composition of the Krebs solution was (in mM) NaCl, 118; KCl, 4.7; $MgSO_4$, 1.2; KH_2PO_4, 1.2; glucose 10; $NaHCO_3$, 24; $CaCl_2$, 2.54. The solution was continuously gassed with 95% O2 and 5% CO_2 to give a pH of 7.4 and was maintained at 37°C. Preparation of tissue and measurement of contractility and setup of the equipment. 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. Isometric tension forces were recorded using a force transducer (SI-KG20, World Precision Instruments, Inc. 175 Sarasota Center Boulevard, Florida 34240-9258, USA), designed for the in vitro study in standard pharmacological experiments for measuring contraction force response of isolation muscle preparations. The organ chamber (20 ml) was part of the experimental setup, as shown in (Figure 2). For further details of setup of the recording system is given in the text.

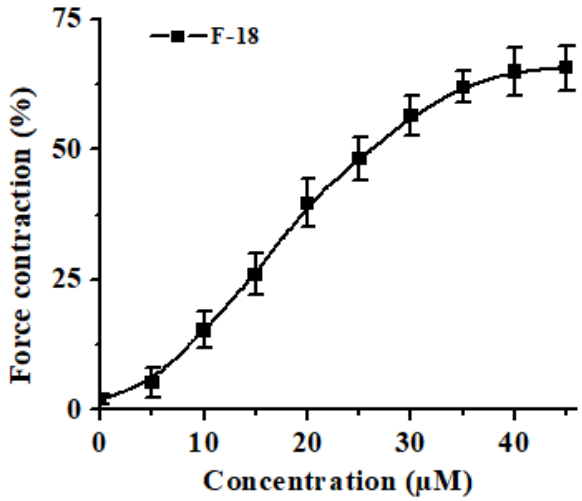

Figure 2: Positive inotropic effect of isoquinoline alkaloids.
The ordinate axis shows the pulsating force of the papillary muscle, expressed as a percentage of the maximum value of 100%. The stimulation frequency is 0.5 Hz (t=+36±0.5°C). P<0.01 (n=6).

The Isometric force transducer SI-KG20 is connected to a transducer amplifier (SI-BAM21-LCB, WPI, Inc. 175 Sarasota Center Boulevard, Florida 34240-9258, USA). The papillary muscle was lifted with electric impuls that was higher than threthold (-20%), rectangular, electrical pulses of frequency 0.5 Hz; 5-10 msec and 5 V amplitude, delivered via a pair of platinum electrodes placed in the muscle-mounting organ chamber by using stimulator ESL-2 (Russia).

Drugs and Reagents

The derivative of isoquinoline alkaloid 1-(2′-bromine-4′,5′-dimethoxyphenyl)-6,7-dimethoxy-1,2,3,4- tetrahydroisoquinoline (F-18) was synthesized by the Bischler-Napieralski cyclization with 3,4-disubstituted phenethylamine and aromatic acetic acid as starting materials in Institute of Plant compounds Uzbek Academy of Sciences. Nifedipine, lidocaine were purchased from Sigma-Aldrich Chimie (Sigma, St. Louis, MO, U.S.A.). 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).

Result And Discussion

The large number of data received in recent years testifies to the development of energy metabolism in cardiomococytes to play a leading role in the development of pathological processes in the heart. It causes dysfunction of the ryanodine receptor (RyR2), sarcoplasmic reticulum Ca^{2+} ATPaseis (SERCA2a), Na^{+}/ Ca^{2+} exchanger in the absence of ATF [7]. When we tested the dose-dependent effect of the F-18 alkaloid on rat heart papillary muscle contraction activity, it was found that this alkaloid had a positive inotropic effect at all concentrations. Initially, the F-18 alkaloid showed no significant effect on the contraction force of papillary muscle from 1 μM to 5 μM, and a positive inotropic effect from 5 μM was observed. The F-18 alkaloid was found to have a maximal effect at 45 μM and an increase in muscle contraction force relative to control - 65.6±4.4% (Figure 2). The semi-maximum effective concentration (EC_{50}) of the alkaloid F-18 was 14.6 μM, respectively.

It is known that the basis of the inotropic effect of various pharmacological agents on myocardial contractile activity lies in the change in the amount of [Ca^{2+}]in cardiomyocytes, which occurs through the modulation of the activity of various Ca^{2+}-transport systems [8]. One of the main causes of positive inotropism is due to the modulation of Ca^{2+}_{L} -channel activity in cardiomyocytes and, in turn, the change [Ca^{2+}]in. In subsequent experiments, the positive inotropic effect of the alkaloid F-18 on the activity of the potential-activating Ca^{2+}_{L} -channel located in the cardiomyocyte sarcolemma was carried out in the presence of a specific blocker of the $Ca2+_{L}$ -channel - nifedipine (IC50-0.01 μM). It was found that the positive inotropic effect of F-18 (45 μM) in the presence of nifedipine 0.01 μM in the medium was 21.7±3.8%, respectively, relative to the control (Figure 3).

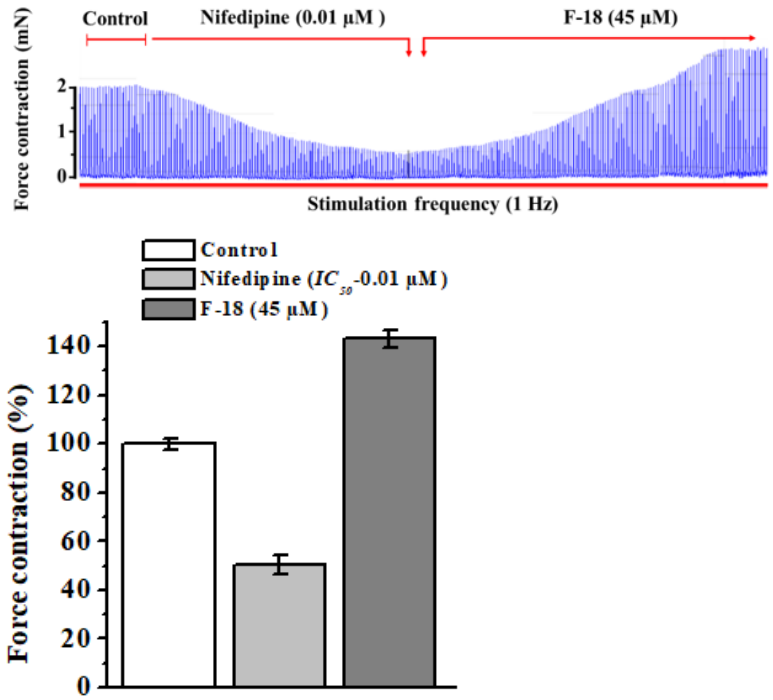

Figure 3: Comparison of the inotropic effects of F-18 alkaloid and nifedipine on the contraction force of extracted rat papillary muscle. **Stimulation:** 0.5 Hz, 5 V, 5 msec, +36±0.5°C, resting tension = 10 mN. P<0.05 indicates value compared to control (n=5).

From this experiment, it can be concluded that the positive inotropic effect of the alkaloid F-18 indicates a low involvement of potential-dependent activating $Ca^{2+}{}_{L}$–channels located in the cardiomyocyte sarcolemma, as well as the presence of other mechanisms. Ca^{2+} ions from SR play an important role in the process of contraction of the heart muscle. In subsequent experiments, the effect of the F-18 alkaloid on the positive inotropic effect on SR Ca^{2+} concentration was studied. The post-rest potency method was used to assess the effect of SR Ca^{2+}. The process of post-rest potentiation is explained by a sharp increase in the initial contraction force when this heart muscle excitation is stopped for 30 seconds and resumed after a certain period of rest. After 30 seconds of rest, cardiomyocytes accumulate more Ca^{2+} ions than in the previous physiological order of SR, and more Ca^{2+} ions are released into the cytosol when reactivation is given. In this case, a sharp increase in the initial contraction force is observed. Post-rest potency is an adequate method widely used in the study of changes in SR Ca^{2+} concentration in cardiomyocytes [9].

In our control experiments, the amplitude of the first contraction force was set to 100% when the papillary muscle stimulation was stopped for 30 s and returned to the previous excitation. Under these conditions, the F-18 alkaloid was found to increase the post-rest potency value by 157.4±4.1% relative to the control under the influence of 45 μM (Figure 4). According to the analysis of the results of this experiment, it can be assumed that the positive inotropic effect of the alkaloid F-18 increases the concentration of $[Ca^{2+}]i$ in cytosol by activating SR function. Data are reported as mean ± SEM (n=5) and expressed as a percentage of control contraction, obtained in normal Krebs solution at 0.1 Hz before the addition of drugs, which was taken as 100%. $P < 0.05$ vs baseline.

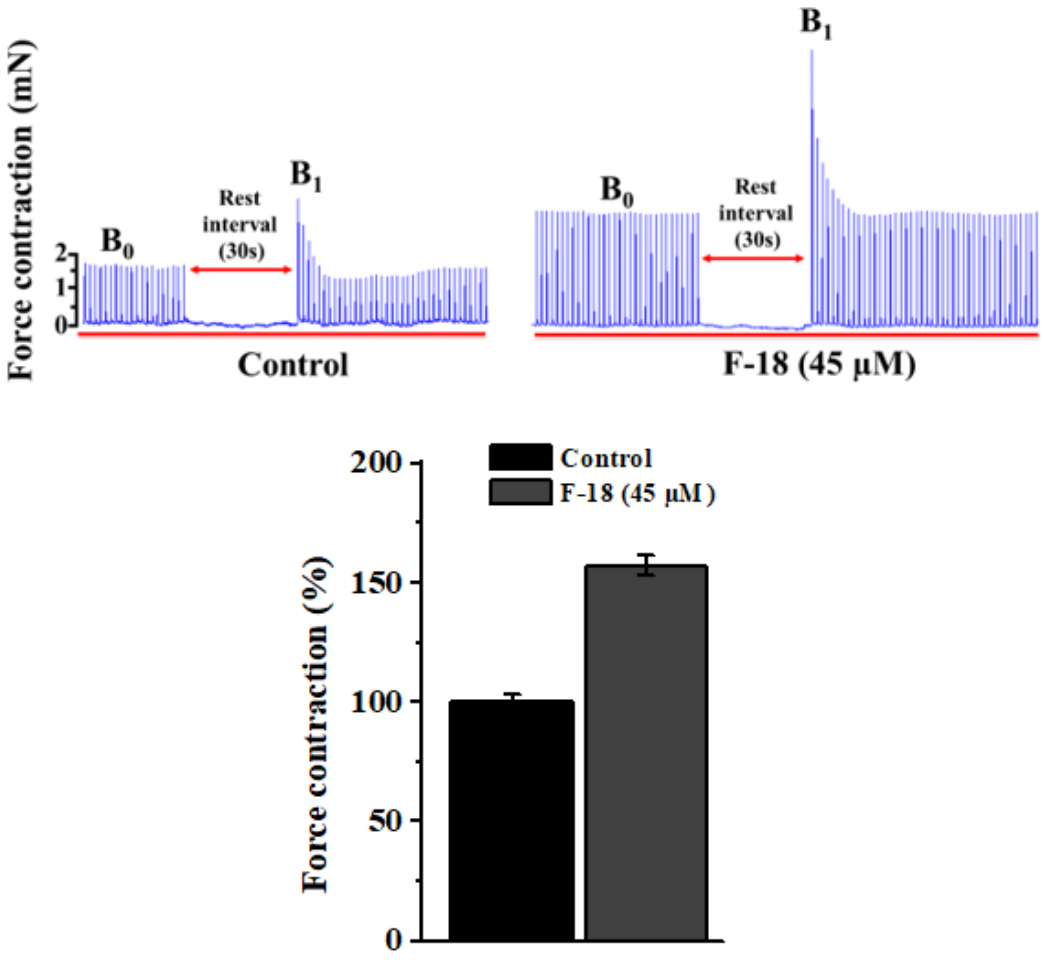

Figure 4: The effect of F-18 on the post-rest potentiation of contraction in rat papillary muscle. (A, B) Representative tracing shows the development of post-rest potentiation of contraction after 30 s rest period in the absence (A) and presence (B) of F-18 (45μM). (C) The relative potentiation of contraction before and after administration of 45 μM F-18.
Data are reported as mean ± SEM (n=5) and expressed as a percentage of control contraction, obtained in normal Krebs solution at 0.1 Hz before the addition of drugs, which was taken as 100%. $P < 0.05$ vs baseline.

Conclusion

All of the above experiments show that the positive inotropic effect of the alkaloid F-18 partially affects the potential-activating Ca^{2+}_{L}-channels located in the cardiomyocyte sarcolemma and mainly affects the SR function, increasing the amount of Ca^{2+}_{L} ions released, resulting in post-rest potency in papillary muscle an increase in the value is observed. The positive inotropic effect of the F-18 alkaloid is explained by its effect on SR by increasing the amount of Ca^{2+} ions accumulated and excreted.

Acknowledgement

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Conflict of Interest

No conflict of interest.

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