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Hypotensive Effect Of The Plant Alkaloid Digitaalisen On The Functional Activity Of Mmc Aortic Chrysallida Of Dihydroemetine On The Functional Activity Of Smc In The Aorta Of The Rat

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ABSTRACT

Effect of dihydroatizin (5–250 µmol / L) on the contractile activity of rat smooth aorta muscle cells (SMC). Isometric tensile forces were recorded. Using a force transducer FT - 03 (Grass Instrument Co., USA). In it was found by experiments that the vasodilating effect of dihydroatizin mainly associated with the blockade of the Ca2 + L-channel.

Methods-Preparation of the aortic vessel muscle preparation, and recording the force of contraction.

Results- KCI-induced contraction of the aortic MMC is associated with the activation of potential–dependent Ca2+L channels of the plasma membranes of the MMC

Conclusions- The data obtained as a result of studying the mechanisms of action of the alkaloid dihydroathysine are of great practical importance and can be recommended for optimizing the process of purposeful creation of a new generation of vasorelaxant drugs.

KEYWORDS

SERCA – SR Ca2+–Atphase; NCX – Na+/Ca2+–exchanger; eNOS – endothelial NO–synthase; MLCK – MLC kinase;

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INTRODUCTION

Nowadays, according to the statistics of the World Health Organization (WHO), there is a wide spread of diseases of the cardiovascular system on a global scale, and they are one of the most urgent medical, social, and economic problems of a global scale[1]. In turn, the creation of new pharmacological preparations with a low level of toxicity compared to synthetic analogues based on natural plant raw materials, which have an effective cardiovascular therapeutic effect, is of urgent importance.

Diterpenoid alkaloids have been proven as promising sources in the research centers of the world in the development of pharmacological preparations for the treatment and prevention of diseases of the cardiovascular system. The development of new effective pharmacological drugs used in clinical practice is a priority and relevant direction in the pharmaceutical industry, especially in the development and production of new antihypertensive drugs from local medicinal plant raw materials. Currently, significant reforms have been implemented in the republic in the direction of prevention and treatment of diseases of the cardiovascular system[2]. On a national scale, large-scale scientific research is being conducted in the direction of diterpenoid alkaloid chemistry, in particular, diterpenoid alkaloids have been isolated from local plant species, their pharmacological activity has been chemically identified and studied.

The aim of this study was to study the effect of the diterpenoid alkaloid Dihydroathysine isolated from Aconitum zeravshanicum plants on the contractile activity of rat aortic SMC.

MATERIAL AND METHODS

In the course of the study, standard physiological methods were used, in particular, in vitro registration of the isometric contractile activity of the blood vessel preparation (mechanography), by the method of inhibitory analysis. [3]. The mathematical and statistical analysis software package OriginPro v. 8.5 SR1 (EULA, Northampton, MA 01060-4401, USA) was used to process the obtained data (Figure 1).

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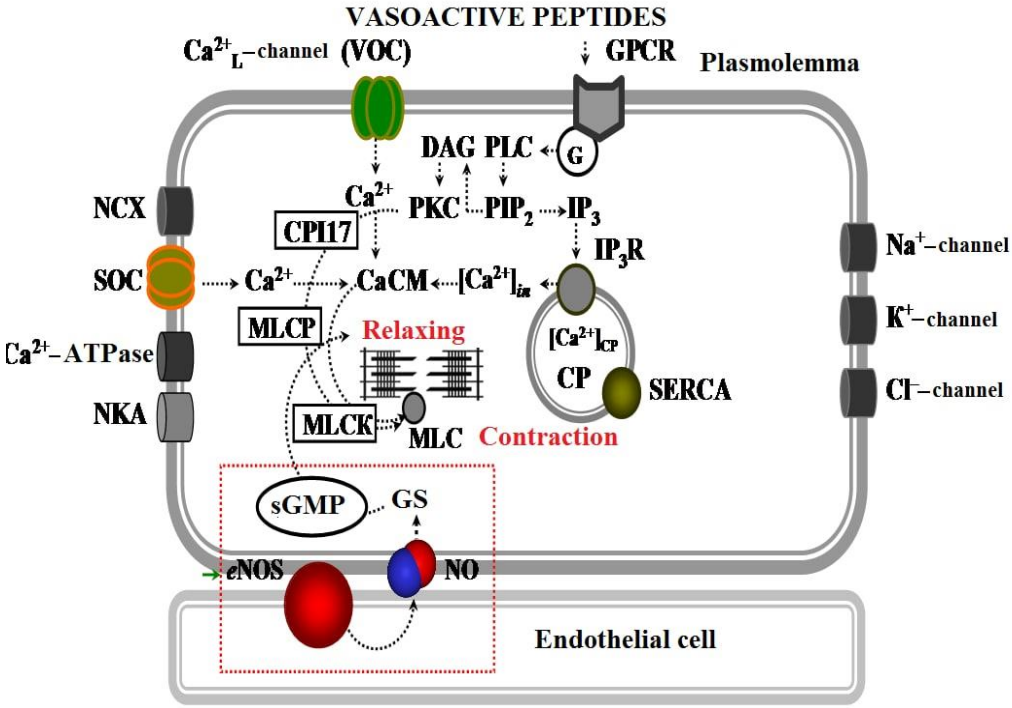

Figure 1. The vascular wall is an ion–transport system, which plays an important role in the functional activity of the smooth muscle cell.

Here [Ca2+]concentration of Ca2+ in – cytosol; SERCA – SR Ca2+–Atphase; NCX – Na+/Ca2+–exchanger; eNOS – endothelial NO–synthase; NO – nitrogen oxide; Gts – guanylatsiklaza; sGMF – cyclic guanosine monophosphate; calmodulin kinase active under the influence of Samk – Sa2+ ions; MLC – miosine light chain; ang II – angiotensin II; ET–1 – endothelin–1; plc – phospholipase C; Dag – diacylglycerol; IP3 – inozitol–3–phosphate; VOC – potential–dependent SA2+L-channels; SOC-Reserve-launching Sa2+ - channels; MLCK – MLC kinase; GPCR – G protein–dependent receptor; IP3R–inozitol – 3–phosphate resorption; PIP2 – Phosphaditilinozitol 4,5-bisphosphate; mlcp-MLC represents phosphatase.

The experiments were carried out on preparations consisting of rings ~3-4 mm wide, isolated from the aorta of white mongrel rats (150-200 g) and placed in a special chamber (5 ml) perfused with krebs–henseleit saline solution. The contractile activity of MMC was studied by mechanography. to register contractile activity, the aortic rings were suspended on one side from the fixed hook of the cell, and on the other side from the lever of the ft–03 force sensor (grass instrument co., usa). before the experiment, the aortic segments were pre-stretched with a load of 1 gy. (~9.8 mn) and washed with saline solution for ~45-60 minutes to achieve equilibrium. Before starting the experiments, the rat aortic MMC preparations were washed with Krebs–Henseleit saline solution for ~45-60 minutes, after which they caused contraction with hyperkalium solution (KCl 50 microns) [3]. At the same time, the amplitude of contractile responses to the action of KCl (50 microns) was considered a control and was taken as 100%. Krebs–Henseleit saline solution contained (mm): NaCl-158.3; KCl-4; CaCl2×2H2O-2;

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MgCl2×2H2O-1.5; NaHCO3 – 10; NaH2PO4×H2O – 0.42; glucose – 5.6 (pH=7.4). The solutions were oxygenated with carbogen (O2-95%, CO2-5%), the solution temperature was maintained at +37±0.5°C using the U–8 ultrathermostat (Bulgaria). Statistical data processing was performed using the OriginLab OriginPro v. 8.5 SR1 application software package (EULA, Northampton, MA 01060-4401, USA) [6].

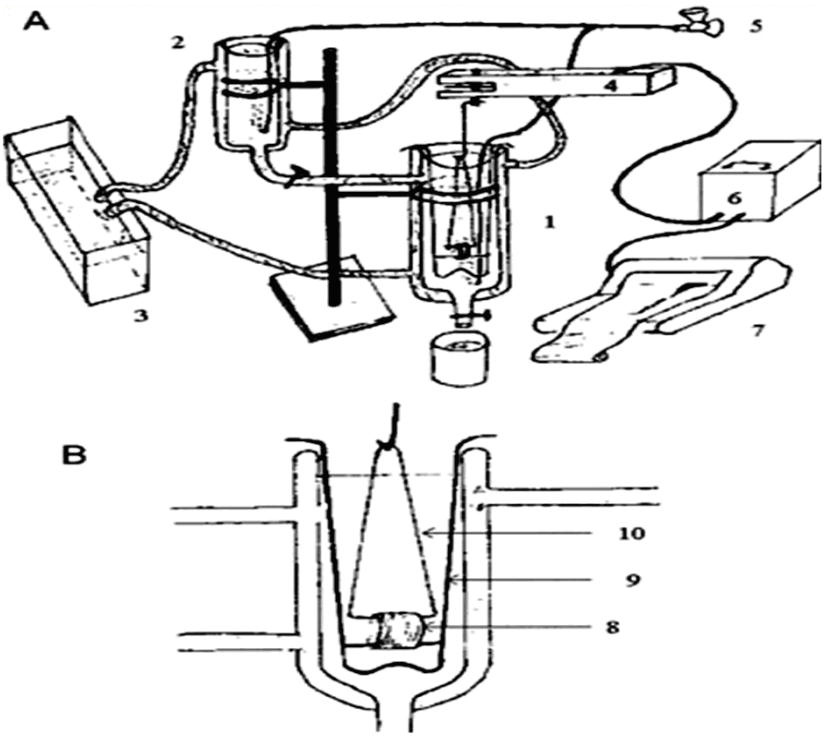

Figure 2. General scheme of the device for recording the contractile activity of the smooth muscles of the rat aortic vessels under isometric conditions.

In this case, A test device in a special container with a volume of 5 ml (1) is placed in a saline solution (2), and the constant temperature of the physiological solution is provided by a thermostat (3). Also a solution of 95% O2 with a gas mixture containing 5% CO2 (5), a device for measuring mechanical activity (4) connected to the device Endim 621.02 (7) through the

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signal amplifier (6). V represents a single drug smooth muscle of the aorta (8) attached to the fixed hook (9), and the other to the hook mekhanotron (10).

RESULTS AND DISCUSSION

In conditions of contraction of the aortic preparation caused by hyperkalium solution (KCl 50 mm) digiroathysine at 5 microns caused aortic drug relaxation by 20.4±4.3%, and at higher concentrations (100 microns) by 76.7±5.2% (n=4-8). under these conditions, the value of ec50 (concentration causing suppression of the contraction force by 50%) for dihydroathysine was 35.6 microns or pd2 (-log50)=4,494. however, in experiments, it was found that the vasorelaxant effect of the alkaloid dihydroathysine was significantly suppressed by verapamil (0.01 microns), a specific Ca2+l – channel blocker. It is known that KCl-induced contraction of the aortic MMC is associated with the activation of potential–dependent Ca2+L channels of the plasma membranes of the MMC [6].

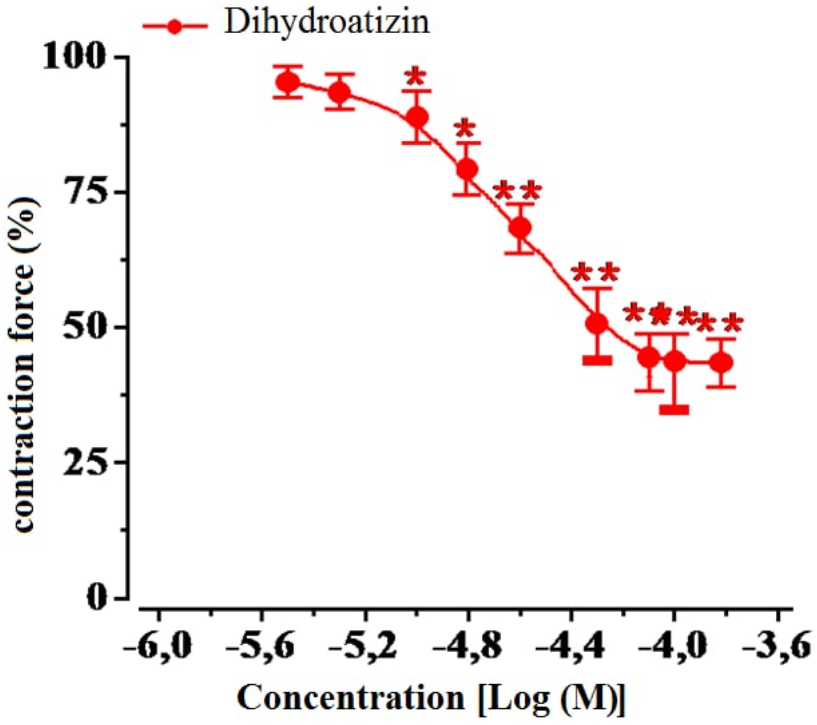

Figure 3. Concentration-dependent vasorelaxant effect of diterpenoid alkaloid dihydroathysine on contractile activity induced by KCl (50 mm) in rat aortic preparation. Contractile force induced by csl (50 mm) is accepted as a control (100%) (* – *p*<0,05; **p<0,01; *n*=4–6).

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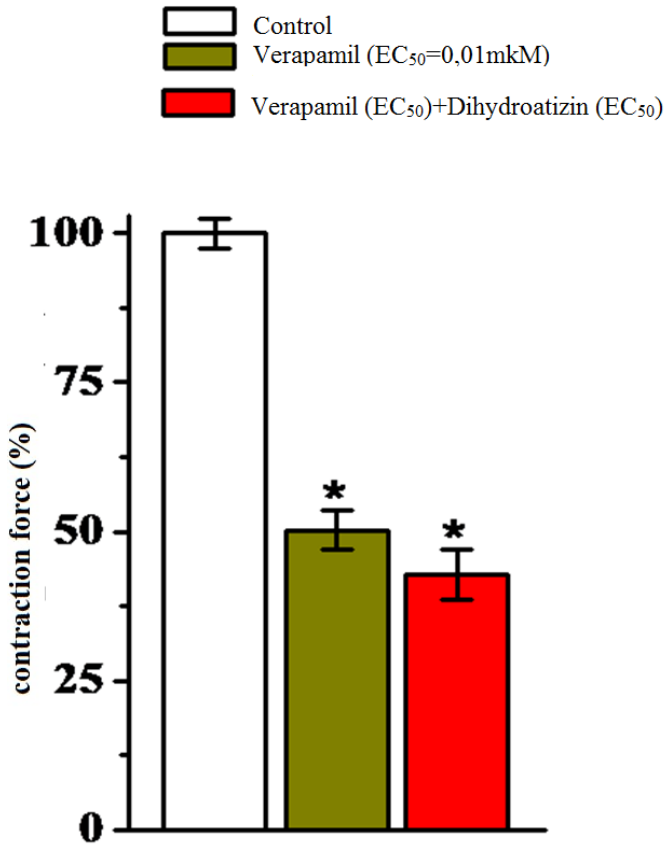

Figure 4. Vasorelaxant effect of the alkaloid dihydroathysine on the contractile activity of the rat aortic preparation induced by the Ca2+L–channel blocker verapamil (EC50=0.01 μm). Contractile force induced by csl (50 mm) is accepted as a control (100%) (* – *p*<0,05; ***p*<0,01; *n*=4–6).

CONCLUSIONS

Thus, it is shown that dihydroathysine has a pronounced vasorelaxant effect, which may be based on its ability to modify the properties of Ca2+L-channels of plasma membranes of MMC. The data obtained as a result of studying the mechanisms of action of the alkaloid dihydroathysine are of great practical importance and can be recommended for optimizing the process of purposeful creation of a new generation of vasorelaxant drugs.

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