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EFFECTS OF NEUROPEPTIDE Y ON ELECTRICAL ACTIVITY AND MYOCARDIAL CONTRACTILITY

A.A. Zverev [a], *T.A. Anikina* [a], *N.G. Iskakov* [a], *A.V. Krulova* [a], *P.M. Masliukov* [b], *J.P. Timmermans* [c], *T.L. Zefirov* [a]

[a] *Kazan Federal University*, *Kazan*, *420008 Russia*
[b] *Yaroslavl State Medical University*, *Yaroslavl*, *150000 Russia*
[c] *University of Antwerp*, *Antwerp*, *2000*, *Belgium*

Abstract

Neuropeptide Y (NPY) and agonist Leu(31)Pro(34)NPY were used to determine the type of NPY receptors involved in electrical activity and myocardial contraction. The experiments on the electrical activity of the right atrium showed that NPY and the selective agonist had negative inotropic and chronotropic actions through the activation of NPY_1 receptor. The activation of NPY-receptors of right atrial cardiomyocytes with NPY leads to a change of the membrane potential and the amplitude-time parameters of the action potential. The experiments with the myocardial strips showed that NPY and the agonist produced the most potent effect at a concentration of 10^{-7} M. At this concentration, Leu(31)Pro(34)NPY showed the greatest positive inotropic effect on the contraction of the atria and ventricles.

Keywords: neuropeptide Y, action potential, contractility, rats

Introduction

Neuropeptide Y (NPY), a 36-amino acid peptide isolated from the pig brain, is structurally characterized by a C-terminal tyrosine amide and N-terminal tyrosine residue. The structures of NPY and NPY mRNA are similar to those of peptide YY (PYY) and pancreatic polypeptide. Therefore, these peptides are called NPY-family peptides, which were derived from the same ancestor [1–3]. NPY has been identified in many animal species. The homology of this bioactive peptide is over 90% among species, and it has been suggested to be conserved from fish to mammals. NPY acts on G-protein-coupled receptors, which have been classified into five subtypes (NPY_1, Y_2, Y_3, Y_4, and Y_5). These receptors are coupled with Gi/o protein and their activation causes a decrease in intracellular cyclic AMP, but it has been shown that they have different affinities for NPY and different distributions in organs [4–6].

NPY is present in both central and peripheral nervous systems. In the central nervous system, NPY neurons occur in the hypothalamus, cerebral cortex, and hippocampus; they regulate pituitary hormone release, appetite, memory, and autonomic nerve functions [6–8]. NPY is co-stored and co-released with catecholamines (noradrenaline and adrenaline) in the peripheral nervous system and is thought to play important roles in the cardiovascular system, such as the regulation of vascular tone and cardiac contractility [9–11]. The effects of NPY on cardiac contractility have been

investigated in many species of mammals (humans, rats, dogs, Guinea pigs, and rabbits) using various experimental approaches (in vivo, isolated heart preparations, and isolated cardiomyocytes).

Various biological effects of NPY and its homologs are mediated by the activation of at least five receptors: Y1R, Y2R, Y4R, Y5R, and Y6R. Among the six NPY receptor subtypes, Y3R subtype has not been cloned, Y6R is a nonfunctional receptor in rat and human [12]. Thus, it seems that Y1R, Y2R, and Y5R are the three major subtypes of NPY receptors that mediate the biological functions of NPY in humans and rats. All known NPY receptors belong to the large superfamily of G-protein-coupled heptahelical receptors [13]. The actions of NPY on peripheral target-organs are predominantly realized through the postsynaptic Y1R, Y5R and the presynaptic Y2R [12, 14, 15].In the heart, the most prominent source of NPY is postganglionic sympathetic fibers, the majority originating from neurons located in the stellate ganglion [16, 17]. In rodents, NPY is also expressed by the parasympathetic neurons of the intrinsic cardiac ganglia [18]. Sensory neurons do not produce NPY under physiological conditions [19–21].

Immunohistochemistry detected Y_1, Y_2, Y_3, and Y_5 receptors in rat endocardium and myocardium [22]. All types of NPY receptors can be pharmacologically discriminated using the appropriate blockers. This approach was especially fruitful in the study of Y_1 and Y_2-receptors. The postsynaptic action of NPY-receptor agonists in the myocardium can have negative or positive inotropic and chronotropic effects [23, 24]. The positive inotropic effect is mediated via Y_1-receptors, L-type Ca^{2+} channels, and mobilization of calcium ions from the sarcoplasmic reticulum [25]. The negative inotropic effect is related to activation of Y_2-receptors and adenylate cyclase inhibition resulting in suppression of Ca^{2+} current [26].

Neuropeptide Y, a sympathetic co-transmitter, has both pre- and post-synaptional actions in the cardiovascular system. It is known that NPY is not a selective agonist for all NPY-receptors. In 1990, a shortened modified C-terminal peptide fragment of NPY, [Leu31, Pro34] NPY, was developed as an agonist for the NPY Y_1 receptor [27]. Y_1 receptors consist of 384 amino acids [28] and are pharmacologically distinguished from Y_1 receptors by their ability to bind [Leu31, Pro34]NPY [27, 29]. Indeed, ligand affinity analysis of a successfully cloned G-protein-coupled receptor enabled identification of Y_1, which binds the NPY family of ligands with the following rank order of potency: NPY = PYY > [Leu31, Pro34] NPY >> PP > PYY13-36 [28]. [Leu31, Pro34] NPY is a selective functional agonist of neuropeptide-Y receptors in rats [27, 30].

Within the cardiovascular system, NPY is found co-localized with noradrenaline in most sympathetic nerve fibers [31]. It is released together with noradrenaline during sympathetic nerve stimulation [32], to act both post- and pre-junctionally. NPY exhibits a variety of acute effects on the cardiac performance, and these involve both pre- and post-junctional sites of action. The post-junctional inotropic and chronotropic effects of NPY, on whole heart or strips of tissues, vary among species and in preparations.

The hearts of several species, including humans, have been shown to exhibit high NPY immunoreactivity and this peptide being more abundant in the atria than in the ventricles [33]. In rodents, NPY immunoreactivity has been reported to be present in sympathetic nerve fibers that innervate coronary arteries and cardiomyocytes [34–36]. High concentrations of NPY were also found in nerve fibers near the sinus and atrio-

ventricular node conductive tissues and in the endocardial layer. Interestingly, NPY is not only present in sympathetic nerve fibers, but also in intrinsic cardiac nerves [37].

Our aim was to study the effects of NPY and related peptides on the regulation of myocardium contractility and electrical activity of atrial preparation and to determine the types of NPY receptors.

Materials and Methods

The experiments were performed on rats aged more than 10–12 weeks and weighing 150–250 g (n = 56) The animals were kept in polycarbonate cages at the temperature of 23 ± 1 °C, relative humidity of 40–60%, and daily light/dark cycle (7:00 am to 7:00 pm). Food and tap water were given ad libitum.

Electrical activity experiments. For experiments with intracellular recording of electrical activity in working myocardium, the rats were decapitated, the chest was rapidly opened. The heart was isolated and washed with Tyrode solution containing (mM): 133.47 NaCl, 4.69 KCl, 1.35 $NaH_2PO_4 \cdot 2H_2O$, 16.31 $NaHCO_3$, 1.18 $MgSO_4 \cdot 7H_2O$, 2.5 $CaCl_2 \cdot 2H_2O$, and 7.77 glucose. The solution was saturated with carbogen (95% O_2, 5% CO_2), pH was maintained at 7.3–7.4 by addition of Trizma base buffer and acid buffer. Isolated right atrial wall or a fragment of the right auricle was washed with Tyrode solution at 39ºC at a rate of 10 ml/min. The myocardial preparations were fixed to the bottom of the chamber with endocardial side turned upwards by Digiscope 2.0 software and a DL-360 linear slave isolator module (Neirobiolab). Intracellular action potentials were recorded via glass microelectrodes with the resistance of 25–60 MΩ. The signals were digitized with an E14-140 converter (L-Card) and recorded using Elph_5p0. The data were processed with AP_Calc. Registration membrane potential (MP), action potential (AP), duration depolarization (DD), amplitude of action potential (A AP), and duration were determined at 20, 50, and 90% repolarization levels (DPD20%, DPD 50%, and DPD 90%).

Contraction experiments. Myocardial contractility was studied in vitro with myocardial strips from albino rats. The contractile function of the myocardium was evaluated after the treatment with NPY and Leu31, Pro34-neuropeptide Y in three increasing concentrations. The study was performed using a PowerLab device (ADInstruments) equipped with a MLT 050/D force transducer (ADInstruments). The hearts were rapidly removed after thoracotomy and maintained in a Petri dish with the working solution under oxygenation and ESL-2 stimulation. Myocardial strips were prepared. The preparation was immersed in Tyrode solution. The strips were stimulated via platinum electrodes (10 pulses/min; pulse duration 5 msec). The results were recorded on a personal computer with Chart 5.1 software. Immersion of the preparations in a reservoir was followed by the “running-in-period” of 40–60 min. Muscle strips gained the optimal tension over this period. Basal contractility was studied over 10 min after the “running-in-period”. Muscle contractility was assayed over 20 min after addition of NPY or Leu31, Pro34-neuropeptide Y in one concentration to the working solution. After NPY stimulation, test preparations were washed 10 times with the working solution for 20 min. Then, basal contractility was estimated for each dose of NPY. The force and duration of NPY-induced contractions were expressed in percent of the basal level.

The following chemicals were used in the experiments: neuropeptide Y, Leu31, and Pro34-neuropeptide Y (Tocris). All chemicals were dissolved in distilled water and applied by micropipette directly into an organ bath.

The results of the experiments are expressed as means ± SEM of at least four experiments using atrial strips from different rats. Statistical significance was assessed by Student's t test for comparison of two groups. AP value of 0.05 or less was considered to be statistically significant.

Results

Electrical activity experiments. The effect of the nonselective NPY receptors agonist neuropeptide Y on the parameters of the membrane potential and action potential at 10^{-8}–10^{-6} M concentrations was investigated. We established that NPY causes a concentration-dependent change in the electrical activity of the myocardium of the right atrium of rats.

NPY at a concentration of 10^{-8} M causes only insignificant changes in the parameters under study.

With the application of NPY at a concentration of 10^{-7}M, pronounced changes in the electrical activity occurred in the rat atrial myocardium. In the preparations working in their spontaneous rhythm, a decrease in the membrane potential and the duration of the depolarization phase by 14% ($p < 0.05$, $n = 9$) was observed against the background of NPY. The amplitude of the action potential increased by 22% ($p < 0.05$). The duration of the action potential by the 15th min at level 20, 50, and 90% of the repolarization phase increased by 9%, 8%, and 10%, respectively (Table 1, Fig. 1).

Table 1. Effect of neuropeptide Y (10^{-7}M) on the electrical activity of the right atrium of the working myocardium

	MP	AAP	DD	DPD 20%	DPD 50%	DPD 90%
Control	–75.2 ± 3.2	98.9 ± 13.2	0.21 ± 0.02	4.3 ± 0.2	7.6 ± 0.2	24.9 ± 3.1
NPY	–64.2 ± 3.4	120.6 ± 11.1	0.18 ± 0.02	4.7 ± 0.2	8.3 ± 0.3	27.6 ± 4.1

The increase in the duration of the action potential was accompanied by a slowdown in the spontaneous rhythm. The frequency of occurrence of the action potential decreased to 7 min from 302 ± 15 to 256 ± 12 per min. ($p < 0.05$, $n = 9$), which is 15% of the original. By the 15th min, the frequency of occurrence of the action potential was 309 ± 21 per min. Thus, in contrast to the parameters of the membrane potential and the action potential, the increase in the frequency of spontaneous activity was short-term and by the 15th min equal to the initial values.

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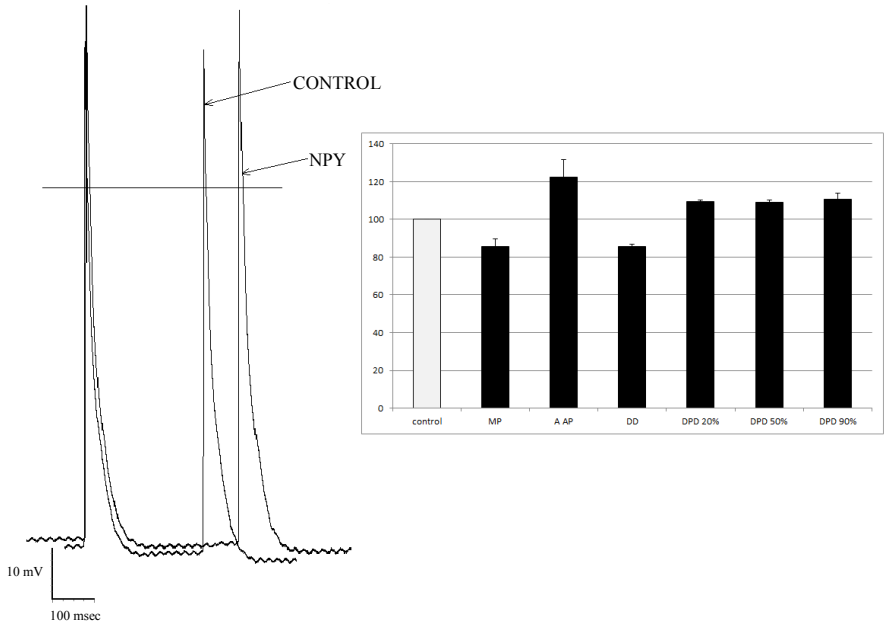

Fig. 1. Effect of neuropeptide Y (10^{-7} M) on the electrical activity the right atrium of the working myocardium

The addition of neuropeptide Y at a concentration of 10^{-6} M caused a decrease in the membrane potential by 12% ($p < 0.05$). The duration of the depolarization phase by the 15th min reduced by 18% ($p < 0.05$). The amplitude of the action potential increased by 23% ($p < 0.05$). The duration of the action potential by the 15th min at the level of 20, 50, and 90% of the repolarization phase increased by 8%, 10%, and 14% ($p < 0.05$).

The frequency of occurrence of the action potential varied unidirectionally and by the 15th min decreased from 296 ± 37 to 183 ± 24 ($p < 0.01$) per min, which corresponds to 38%.

Thus, the activation of NPY-receptors of right atrial cardiomyocytes with NPY led to changes of MP and the amplitude-time parameters of the action potential.

The agonist of NPY_1-receptors, Leo(31)Pro(34)NPY, at a concentration of 10^{-8} M did not cause significant changes in the parameters of the membrane potential and the action potential.

The application of Leo(31)Pro(34)NPY at a concentration 10^{-7} M did not cause any change in the membrane potential and the amplitude of the action potential. The duration of the depolarization phase decreased by 14.7% ($p < 0.05$). The duration of the action potential by the 15th min at the level of 20% of the repolarization phase increased by 19% ($p < 0.05$), at the level of 50% by 13% ($p < 0.05$), and at the level of 90% by 7% ($p < 0.05$).

The frequency of occurrence of the action potential by the 15th min decreased from 285 ± 26 to 256 ± 19 ($p < 0.01$) per min, which corresponds to 10% (Fig. 2).

The agonist of NPY_1-receptors, Leo(31)Pro(34)NPY, at a concentration of 10^{-6} M caused a decrease in the membrane potential by 9% ($p < 0.05$). The duration of the depolarization phase decreased by 19% ($p < 0.05$; $n = 8$). The amplitude of the action

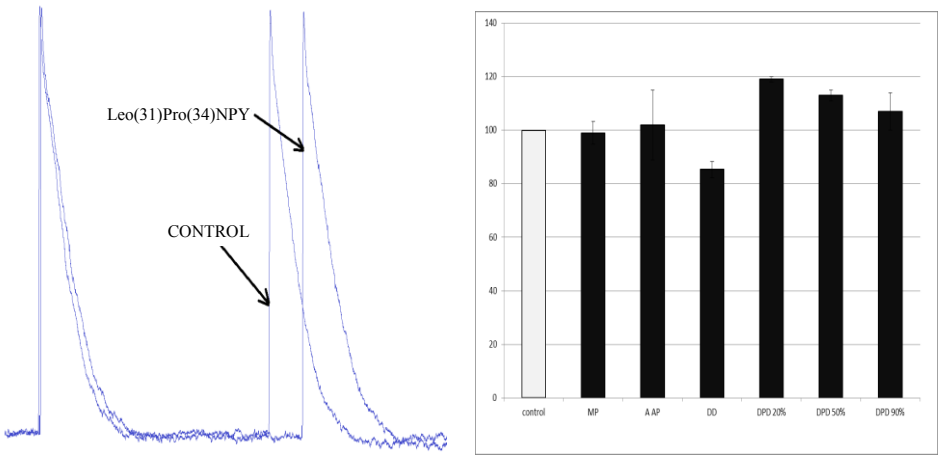

Fig. 2. Effect of Leo(31)Pro(34)NPY (10^{-7} M) on the electrical activity of the right atrium of the working myocardium

potential increased by 4%. The duration of the action potential at the level of 20% of repolarization varied unidirectionally and by the 7th–15th minute phase increased by 19% ($p < 0.05$).

The duration of the action potential at the level of 50 and 90% of the repolarization phase in the 7th min decreased by 32 and 35%, respectively. By the 15th min, it was equal to the initial value of the duration of the action potential at the level of 50% of the repolarization phase.

The frequency of occurrence of the action potential by the 7th min decreased from 282 ± 24 to 246 ± 21 per min, which corresponds to 13% ($p < 0.01$), and was equal to the initial values by the 15th min of the agonist application.

Contraction experiments. The effect of a nonselective NPY agonist on myocardial contractility in rats of various age groups was studied to confirm the presence of functionally active receptors for NPY in the myocardium. NPY at concentrations of 10^{-10}–10^{-6} M had a dose-dependent effect and induced the contraction of myocardial strips from the atria and ventricles of 100-day-old animals.

NPY at the specified concentrations had little effect on the force and duration of contractions of myocardial strips from the atria and ventricles of 100-day-old animals.

To confirm the presence of functionally active NPY_1 receptors in the myocardium, the effect of the selective NPY_1 receptor agonist, Leu(31)Pro(34)NPY, on myocardial contractility in 100-day-old rats was studied in a special series of experiments. This agonist at a concentration range of 10^{-10}–10^{-5} M induced dose-dependent contractions of the atrial and ventricular strips. At a concentration of 10^{-7} M, Leu(31)Pro(34)NPY induced a significant positive inotropic effect on atrial and ventricular myocardial strips, the respective increments of contractile force being $7.7 \pm 3.2\%$ ($p < 0.05$; $n = 10$) and $6.6 \pm 2.8\%$ ($n = 8$). The duration of isometric contraction of both types of the strips did not change significantly. We observed an insignificant increase in contraction time, relaxation rate, and relaxation time accompanied by a decrease in the contraction rate in both the atrial and ventricular strips (Fig. 3).

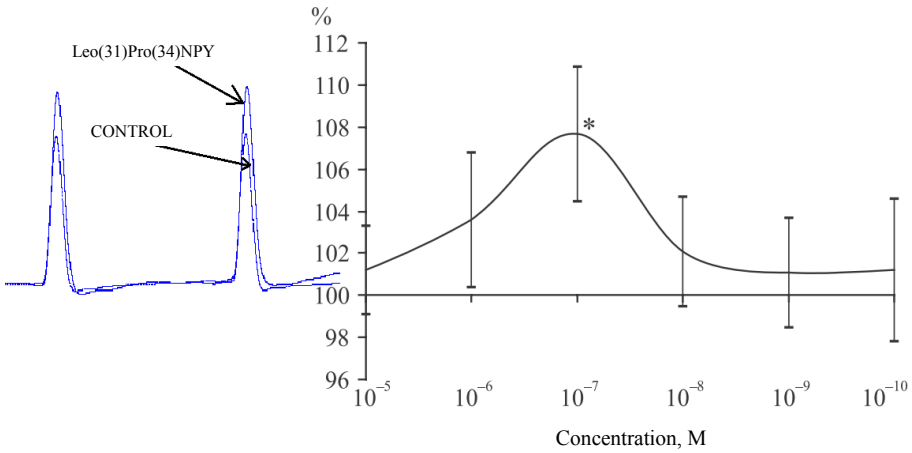

Fig. 3. Effect of Leo(31)Pro(34)NPY (10^{-7} M) on myocardial contractility

The agonist applied at the concentrations of 10^{-10}, 10^{-9}, 10^{-8}, 10^{-6}, and 10^{-5} M produced no significant effect on the parameters of contractile activity of myocardial strips (Fig. 3). At this concentration range, Leu(31)Pro(34)NPY induced no significant changes in the duration of isometric contraction of myocardial strips.

Discussion

The effects of NPY on the cardiac function are mostly similar among species, but sometimes they can differ. Therefore, a comparative biological study is needed for a systematical understanding of NPY functions in the heart. Although, rats are commonly used as experimental animals, there has been no functional study of the effect of NPY on the cardiac contraction in rats.

In the peripheral nervous system, NPY is stored and released along with catecholamine (neurotransmitters of sympathetic nerves) and plays important roles in the cardiovascular system, such as regulation of vascular tone and cardiac contractility, through activation of various pathways, including direct action on cardiomyocytes and regulation of autonomic nervous function (cholinergic and adrenergic neurons).

It is known that many ion channels participate in the formation of the cardiomyocyte action potential. Our data on the reduction of the membrane potential for the application of NPY can be explained by the modification of the K-channels of rest. The change of the amplitude-time parameters of the action potential on the effect of NPY can be explained by a change in the kinetics of the Na- and Ca-cardiomyocytes channels. The delay of the repolarization phase is possibly associated with changes in the kinetics of the potential-dependent K-channels, which lead to a decrease in the total K-current. The change in the frequency of spontaneous rhythm indicates that NPY has an effect on atypical cardiomyocytes, which is possibly related to the modification of Ca-channels and If-currents.

In this study, it was found that NPY has negative inotropic and chronotropic actions through activation of the NPY_1 receptor in the rat atrium. These results suggest that the NPY Y_1 receptor has a regulatory role in the electrical activity and contraction of the rat heart.

We revealed that NPY has negative inotropic actions. The selective Y_1 receptor agonist, Leu31(Pro34)NPY, had positive inotropic actions, because the NPY_1 receptor couples with Gi/o, which is a pertussis toxin-sensitive G protein. The pharmacological evidences indicated involvement of the NPY_1 receptor in the positive inotropic actions.

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Zverev Aleksei Anatol'evich, Candidate of Biological Sciences, Associate Professor, Department of Human Health Protection

Kazan Federal University
ul. Kremlevskaya, 18, Kazan, 420008 Russia
E-mail: *Alekcei5@rambler.ru*

Anikina Tat'yana Andreevna, Doctor of Biological Sciences, Professor, Department of Human Health Protection

Kazan Federal University
ul. Kremlevskaya, 18, Kazan, 420008 Russia
E-mail: *Taniya57vg1@@rambler.ru*

Iskakov Nikita Georgievich, PhD Student, Department of Human Health Protection

Kazan Federal University
ul. Kremlevskaya, 18, Kazan, 420008 Russia
E-mail: *nikitaiskakov1992@mail.ru*

Krulova Alevtina Vasil'evna, Candidate of Biological Sciences, Associate Professor, Department of Human Health Protection

Kazan Federal University
ul. Kremlevskaya, 18, Kazan, 420008 Russia
E-mail: *krylova.alevtina@gmail.com*

Masliukov Petr Mikhailovich, Doctor of Medical Sciences, Professor, Department of Normal Physiology with Biophysics

Yaroslavl State Medical University
ul. Revolyutsionnaya, 5, Yaroslavl, 150000 Russia
E-mail: *mpm@ysmu.ru*

Timmermans Jean Pierre, PhD, Professor, Department of Veterinary Sciences

University of Antwerp
St-Jacobsmarkt 9-13, Antwerp, 2000, Belgium

Zefirov Timur L'vovich, Doctor of Medical Sciences, Professor, Department of Human Health Protection

Kazan Federal University
ul. Kremlevskaya, 18, Kazan, 420008 Russia
E-mail: *zefirovtl@mail.ru*

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Влияние нейропептида Y на электрическую активность и сократимость миокарда

А.А. Зверев[1], *Т.А. Аникина*[1], *Н.Г. Искаков*[1], *А.В. Крылова*[1], *П.М. Маслюков*[2], *Ж.П. Тиммерманс*[3], *Т.Л. Зефиров*[1]

[1]*Казанский* (*Приволжский*) *федеральный университет*, *г. Казань*, *420008*, *Россия*
[b]*Ярославский государственный медицинский университет*, *Ярославль*, *150000*, *Россия*
[c]*Антверпенский университет*, *Антверпен*, *2000*, *Бельгия*

Аннотация

На основе нейропептида Y и селективного агониста Leu (31)Pro(34)NPY установлен тип NPY-рецепторов, определяющих электрическую активность и сократимость миокарда у крыс. Экспериментальное исследование электрической активности правого предсердия крыс показало, что нейропептид Y и Leu (31)Pro (34)NPY оказывают отрицательное инотропное и хронотропное действие посредством активации NPY_1-рецептора. Активация NPY-рецепторов кардиомиоцитов правого предсердия нейропептидом Y приводит к изменению мембранного потенциала и амплитудно-временных параметров потенциала действия. Опыты с полосками миокарда показали, что наиболее сильное действие нейропептида Y и Leu (31)Pro(34)NPY наблюдалось при концентрации 10^{-7} М. В этой концентрации Leu(31)Pro(34)NPY имел наибольший положительный инотропный эффект на сокращение предсердия и желудочков.

Ключевые слова: нейропептид Y, потенциал действия, сократимость, крысы

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Зверев Алексей Анатольевич, кандидат биологических наук, доцент кафедры охраны здоровья человека

Казанский (Приволжский) федеральный университет
ул. Кремлевская, д. 18, г. Казань, 420008, Россия
E-mail: *Alekcei5@rambler.ru*

Аникина Татьяна Андреевна, доктор биологических наук, профессор кафедры охраны здоровья человека

Казанский (Приволжский) федеральный университет
ул. Кремлевская, д. 18, г. Казань, 420008, Россия
E-mail: *Taniya57vg1@@rambler.ru*

Искаков Никита Георгиевич, аспирант кафедры охраны здоровья человека

Казанский (Приволжский) федеральный университет
ул. Кремлевская, д. 18, г. Казань, 420008, Россия
E-mail: *nikitaiskakov1992@mail.ru*

Крылова Алевтина Васильевна, кандидат биологических наук, доцент кафедры охраны здоровья человека

Казанский (Приволжский) федеральный университет
ул. Кремлевская, д. 18, г. Казань, 420008, Россия
E-mail: *krylova.alevtina@gmail.com*

Маслюков Петр Михайлович, доктор медицинских наук, профессор кафедры нормальной физиологии с биофизикой

Ярославский государственный медицинский университет
ул. Революционная, д. 5, г. Ярославль, 150000, Россия
E-mail: *mpm@ysmu.ru*

Тиммерманс Жан Пьер, доктор наук, профессор кафедры ветеринарии

Антверпенский университет
Ст-Якобсмаркт 9-13, г. Антверп, 2000, Бельгия

Зефиров Тимур Львович, доктор медицинских наук, профессор кафедра охраны здоровья человека

Казанский (Приволжский) федеральный университет
ул. Кремлевская, д. 18, г. Казань, 420008, Россия
E-mail: *zefirovtl@mail.ru*

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