Research Article

New Antiarrhythmic Agent to Stabilize Functional Activity of Rat Heart Sinus Node Cardiomyocytes

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Abstract

Introduction: The aim of this study was to explore the antiarrhythmic activity of the new antiarrhythmic drug, succinic acid ester of 5-hydroxyadamantane-2-one (ADK-1110) and its effect on the functional activity of rat heart sinus node.

Materials and methods: Experiments were performed on 80 non-linear white awake male rats weighing 200 g, using calcium chloride and aconitine arrhythmia models. The ECG was recorded from all the animals in the II standard lead before the start of the experiment. The effect of ADK-1110 on the electrical activity characteristics of rat heart sinus node pacemakers in vitro was studied on 26 outbred Wistar rats of both sexes with a body weight of 160 to 200 g, using the microelectrode technique.

Results and discussion: The compound significantly exceeds the known reference drugs in terms of the antiarrhythmic index. The agent also surpasses our previously proposed adamantane derivative ADK-1100 on calcium chloride model and is not inferior to the aconitine one. The electrophysiological analysis of the sinus node pacemaker cardiomyocytes characteristics in vitro under the influence of ADK-1110 revealed that the compound expands the area occupied by true pacemakers.

Discussion: The obtained data indicate the presence of properties of antiarrhythmics of classes I, III, and IV in ADK-1110. The indicated functional remodeling stabilizes the functional activity of the central part of the sinus node.

Conclusion: ADK-1110 stabilizes the functional activity of the central part of the sinus node. ADK-1110 also has a cerebrovascular anti-ischemic property.

Keywords

Introduction

Modern practical medicine has a serious need for the development of new antiarrhythmic drugs with a high antiarrhythmic activity, no pro-arrhythmogenic effects and low toxicity. It is known that for the most common types of arrhythmias, such as atrial fibrillation, class III drugs (by Vaughan-Williams's classification) are effective. These include cardiocyclide, nibentan, refralon (niferidil), sotalol and vernacalant (Camm et al. 2011; Glushkov et al. 2011; Mironov et al. 2012; Turilova et al. 2012; Maykov et al. 2015). At the same time in clinical practice while treating cardiac arrhythmias, the combination therapy including antiarrhythmic drugs of various classes is used most often (Maykov et al. 2015).

However, the antiarrhythmic drugs are often not effective enough and have serious side effects, including proarrhythmogenic effects (Pollard et al. 2010).

Earlier, among adamantane derivatives, we discovered a new agent for the treatment of arrhythmias -N-[2-(adamant-2-yl)aminocarbonylmethyl]-N'-[3-(diethylamino)propyl]-4-nitrobenzamide (ADK-1100), which has an advantage over a number of known antiarrhythmic drugs (Avdyunina et al. 2019). It has been established that the ADK-1100 has a pronounced antiarrhythmic (antifibrillary) activity on calcium chloride and aconitine arrhythmias. It also has low toxicity, and, in terms of the breadth of its therapeutic effect, it surpasses the well-known antiarrhythmic drugs of class I (lidocaine, ethmosine, novocainamide), class III (cardiocyclide), and class IV (verapamil).

Further, among the adamantane derivatives, we revealed a new compound – succinic acid ester of 5-hydroxyadamantane-2-one (ADK-1110), which has a pronounced cerebrovascular anti-ischemic activity and does not have a hypotensive effect (Kurza et al. 2018). Given the previously identified ability of the adamantane derivative (ADK-1100) to exert an antiarrhythmic effect, it seemed important to investigate the possibility of another derivative of adamantane (ADK-1110) having these properties.

The main source of rhythmic contractile activity of the heart is the sinus node pacemaker cells (pacemakers) (Boyett et al. 2000; Dobrzynski et al. 2007; Yanni et al. 2010). Normally, there is some number of subsidiary pacemakers in the right atrium (Rozanski and Lipsius 1985), which, due to a number of pathological changes, can intercept the leading function from the true pacemakers of the sinus node and will lead to the development of arrhythmia, and more often – tachyarrhythmia.

The closest experimental animal to the human organization of the sinus node is a rat (Sutiagin 2009). Electrophysiological mapping of the rat heart sinus node from both epicardial and endocardial surfaces revealed the multicluster (or multicentric) nature of the localization of true pacemakers within the sinus node. The gaps between clusters of true pacemakers are filled with latent pacemakers with various characteristics of electrical activity (Rodina et al. 2019). All of the above led us to the choice of the rat heart sinus node as a test object for studying the antiarrhythmic activity of ADK-1110 in vitro.

The aim of this study was to explore the antiarrhythmic activity of ADK-1110 and its effect on the functional activity of rat heart sinus node.

Material and methods

The experimental material was obtained on white rats kept under standard vivarium conditions. Care for rats was carried out in accordance with the current Russian legislation and the Guide for the Care and Use of Laboratory Animals, National Academy Press, USA 2011. Throughout maintenance, they regularly received standard food and drink without restrictions.

Experiments on the study of the antiarrhythmic activity of ADK-1110 were performed on 80 non-linear white awake male rats weighing 200 g.

Acute toxicity of the substance was studied in nonlinear awake male rats weighing 200 g with intravenous administration. Pyrogen-free water for injection was used as a solvent. The study of acute toxicity was carried out on 6–8 animals, using three or more doses. The results were evaluated 2 weeks after administration of the compounds. The effective dose – ED_{50} – and the lethal dose – LD_{50}, as well as confidence limits, were calculated by the method of Miller and Tainter at a probability level of $p = 0.05$.

Two models of arrhythmias were used in the work: calcium chloride and aconitine (Galenko-Yaroshevsky et al. 2012).

When studying the antiarrhythmic activity before the start of the experiment, the ECG was recorded from all the animals in the II standard lead.

Calcium chloride arrhythmia was caused by high doses of a 10% solution of calcium chloride (250–390 mg/kg). 1–2 minutes after the administration of calcium chloride, ventricular fibrillation occurs. At the beginning of the experiment, a dose of 10% calcium chloride solution was selected, causing lethal ventricular fibrillation. The test compounds were administered 1–2 minutes before the administration of calcium chloride. The ECG was recorded in the II standard lead every 5 minutes, using Polyspectra-8/B and a computer program. The antiarrhythmic effect was evaluated by reducing the number of cases of lethal ventricular fibrillation of the heart. The significance of the data was evaluated using.

Aconitine arrhythmia was caused by intravenous administration of aconitine hydrochloride at doses of 30–40 µg/kg. 1–3 minutes after the administration of aconitine, cardiac arrhythmias of a mixed atrioventricular type developed, which were diverse. In the experiments, a dose of aconitine, which caused heart rhythm disturbances (polytopicextrasystole) of moderate severity, was used. The ECG was recorded in II standard lead using Polyspectra-8/B and a computer program 3, 5, 10, 15, and 20 minutes after administration of aconitine. The criterion for the positive effect of the compound was the absence of

arrhythmia caused by aconitine. The effective dose (ED_{50}) and confidence limits were calculated by the Miller and Tainter's method at a probability level of $p = 0.05$. The therapeutic index window of the drug was judged by the antiarrhythmic index, which is the ratio of the lethal dose LD_{50} to effective dose ED_{50}.

The animals of this series of experiments were divided into the following experimental groups: 1 – study of the acute toxicity of succinic acid ester of 5-hydroxyadamantan-2-one ($n = 21$); 2 – study of the effect of succinic acid ester of 5-hydroxyadamantan-2-one on heart rhythm disturbances caused by calcium chloride ($n = 32$); 3 – study of the effect of succinic acid ester of 5-hydroxyadamantan-2-one on heart rhythm disturbances caused by aconitine ($n = 27$).

The study used the following substances: succinic acid ester of 5-hydroxyadamantan-2-one (ADK-1110, experimental and technological department of V.V. Zakusov Research Institute of Pharmacology, Russia); N-[2-(adamant-2-yl)aminocarbonylmethyl]-N'-[3-(diethylamino)propyl]-4-nitrobenzamide (ADK-1100, service division of V.V. Zakusov Research Institute of Pharmacology, Russia); cardiocyclide (service division of V.V. Zakusov Research Institute of Pharmacology, Russia), which were injected intraperitoneally.

The effect of ADK-1110 on the electrical activity characteristics of rat heart sinus node pacemakers in vitro was studied on 26 outbred Wistar rats of both sexes with a body weight of 160 to 200 g.

The rats were anesthetized with an intraperitoneal injection of a solution of Zoletil (Zoletil 100, Virbac, France) at a dose of 40 mg/kg of body weight and were killed by opening the chest. Then, the right atrium with the auricle, cranial and caudal vena cava was excised, placed in a bath filled with Hanks' solution at room temperature. The obtained preparation was attached with stainless steel needles to the support with the endocardial surface facing up and transferred to a thermostatic flow cell ($t° = 38°$) filled with a Krebs-Ringer solution balanced to pH = 7.40 with a mixture of 5% CO_2 and 95% O_2. The flow rate of the medium through the flow cell was about 3 ml/min. Before studying, the specimen was photographed through the eyepiece of the microscope of an electrophysiological unit, into which an eyepiece-micrometer was inserted (graduation 0.012 mm).The position of the tip of the microelectrode was applied to the photograph of the preparation. The electrical activity of cardiomyocytes was recorded by conventional floating glass microelectrodes filled with 3 M KCl with a resistance of 40–60 mΩ. After five minutes of recording cell action potentials, the Krebs-Ringer solution in the flow cell was replaced with the same one containing ADK-1110. Then we tried to record electrical activity as long as possible. In total, three experimental options were used with the following concentrations of ADK-1110: 5 mg/L, 50 mg/L and sequential administration of 5 mg/L, and then 50 mg/L.

If electrical activity of the sinus node stopped, the preparation was washed with an intact Krebs-Ringer solution.

An Intracellular Electrometer IE-210 (Warner Instruments Co., USA) was used as a DC amplifier. The signal from the output of the DC amplifier through the L-card E-14-140-M analog-to-digital converter was recorded with a sampling frequency of 20 kHz in the POWERGRAPH 3.3 PROFESSIONAL software. For the subsequent analysis, the averaged action potentials were used, obtained by averaging a series of twenty consecutive action potentials with subsequent application of the corresponding noise filters on the averaged potential. Calculation of electrophysiological data was carried out in Peak Analysis extension (v1.2.1) from LABCHART 7.2 PRO software, as well as in AUTOCAD 2012.

The following characteristics of action potentials were subjected to a quantitative analysis (Fig. 1A): Action Potential Amplitude, (APA, mV), Maximal Diastolic Potential, (MDP, mV), Overshoot, (OS, mV), Slow Diastolic depolarization (dV/dt_4, mV/sec), Maximum rate of the first time derivative of the phase-0 upstroke of the action potential (dV/dt_0, V/sec), Radius of transition curvature from Phase 4 to Phase 0 (R_{4-0}, arbitrary units (c.u.) of AUTOCAD 2012 software obtained by analyzing action potential curves with a standardized scan with values of 0.05 sec/div along the abscissa axis and 10 mV/div along the ordinate axis), Action potential rate (F, Hz), and Action Potential Duration, (APD_{70}, msec) at the level of 70% APA.

Statistical processing and graphing were carried out in the GRAPHPADPRISM 6 software. Table 1 shows the values of M (mean)±SEM (standard error of the mean).

Results

The effect of ADK-1110 on heart rhythm disturbances caused by high doses of calcium chloride and aconitine

The study started with examining the acute toxicity of ADK-1110 on non-linear, awake male rats weighing 200 g when given intravenously ($n = 21$). ADK-1100 and cardiocyclide were used as reference drugs. The studies showed that the ADK-1110 turned out to be the least toxic, with LD_{50} being 9–18 times higher than cardiocyclide and ADK-1100, respectively (Table 1). ADK-1110 belongs to the 4th class of toxicity (Sidorov 1973).

Next, we studied the effect of ADK-1110 on heart rhythm disturbances caused by high doses of calcium chloride ($n = 32$). The experiments showed that in the control with the intravenous administration of a 10% solution of calcium chloride (250–390 mg/kg), all the 10 animals died. The protective effect of ADK-1110 was manifested at the doses of 0.5–1.0–2.0 mg/kg when administered intravenously prior to the administration of calcium chloride. Depending on the dose of the studied compounds, the survival rate of animals ranged from 37 to 86%. The surviving animals showed no ECG abnormalities. When determining the antiarrhythmic index of ADK-1110, it was found that the compound exceeded the comparison drugs in terms of antiarrhythmic index – cardiocyclide

A

B
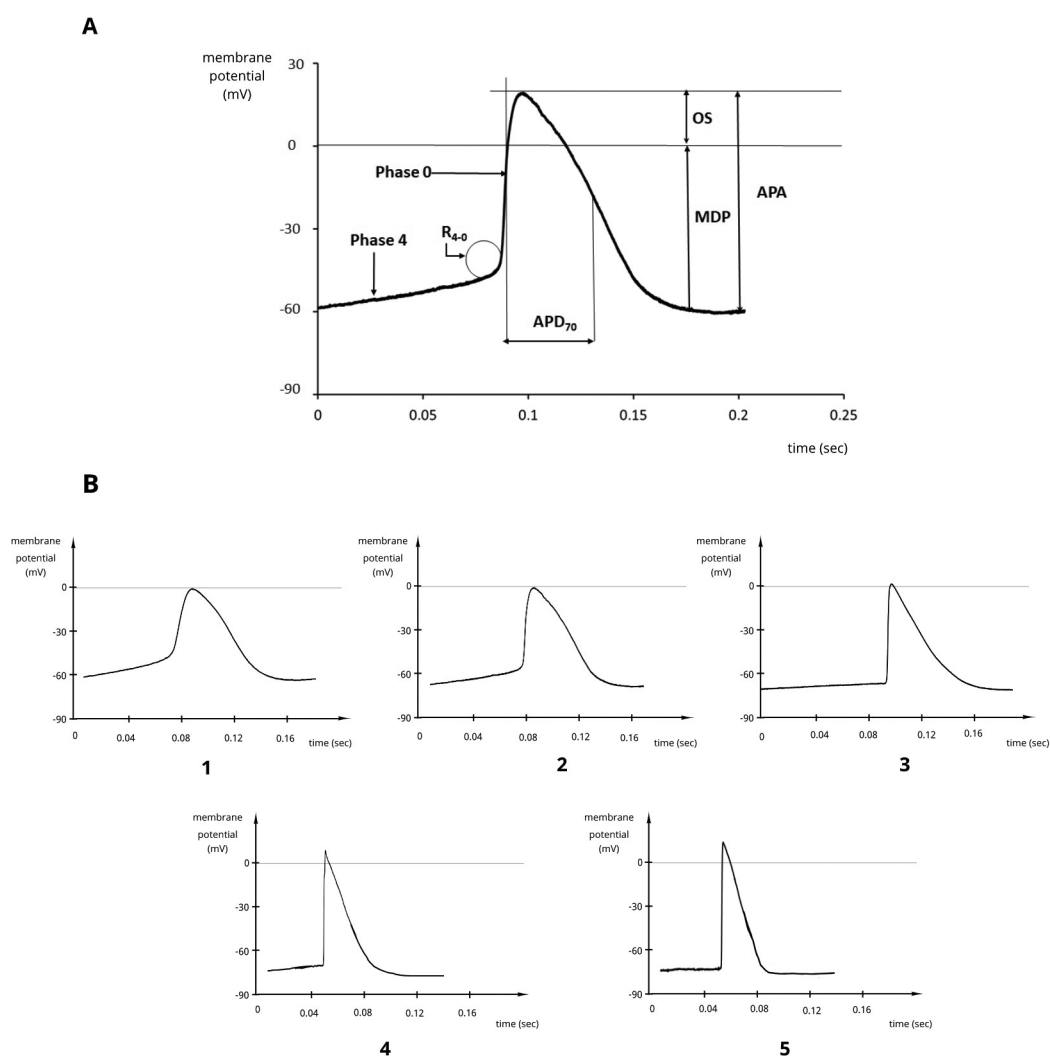
Figure 1. The main electrophysiological characteristics and action potentials of sinus node pacemakers. **Note: A.** The main electrophysiological characteristics of rat heart sinus node pacemakers: Phase 4 – slow diastolic depolarization (dV/dt_4); Phase 0 – upstroke (dV/dt_0); APA – action potential amplitude (APA = MDP + OS); MDP – maximal diastolic potential; OS – overshoot; APD_{70} – action potential duration at the level of 70% APA; R_{4-0} – radius of curvature of transition from Phase 4 to Phase 0. **B.** Action potentials of: 1 – True Pacemakers (TP); 2 – Potential True Pacemakers (PTP); 3 – Transitional Latent Pacemakers (TLP); 4 – Atrial Type Pacemakers (ATP); 5 – Atrial Working Cardiomyocytes (AWC).

(5.5 times), lidocaine (158 times), verapamil (53 times), and ADK-1100 (3.4 times), which indicates its widest therapeutic window (Table 1).

The study of the effect of ADK-1110 on heart rhythm disturbances caused by aconitine ($n = 27$) showed that under these conditions the compound had a significant antiarrhythmic activity, and exceeded the comparison drugs in terms of antiarrhythmic index – cardiocyclide, lidocaine, ethmosine, novocainamide, but was not inferior to ADK-1100 (Table 1).

In this arrhythmia model, ADK-1110 has an advantage over the known antiarrhythmic drugs of class I (ethmosine – 5.1 times, lidocaine – 59 times, and novocainamide – 109 times), class III (cardiocyclide – 1.8 times) and is not inferior to ADK-1100 in terms of the therapeutic window (Table 1).

Thus, the results of the study made it possible to establish that ADK-1110 exhibits the antiarrhythmic activity under the conditions of both calcium chloride- and aconitine-arrhythmia models. The data obtained indicate that this compound has the antiarrhythmic properties of classes I, III, and IV.

Selection of sinus node pacemaker groups for analysis of the effect of 5-hydroxyadamantan-2-one succinic acid ester

An analysis of electrophysiological characteristics of the rat heart sinus node pacemaker cardiomyocytes under normal conditions and under the influence of ADK-1110 made it possible to suggest that there were at least four types of pacemakers within the sinus node (Fig. 1.B, Table 2).

1. True Pacemakers (TPs) are characterized by the maximum values of the radius of transition curvature from Phase 4 to Phase 0 (R_{4-0}) (Fig. 1.B.1,

Table 1. Antiarrhythmic Activity of Succinic Acid Ester of 5-hydroxyadamantan-2-one (ADK-1110) and Reference Agents on Heart Rhythm Disturbances Caused by Calcium Chloride(1) and Aconitine (2)

Agents	ED_{50}- 1	ED_{50}- 2	LD_{50}	Antiarrhythmic index LD_{50}/ ED_{50} -1	Antiarrhythmic index LD_{50}/ ED_{50} -2
ADK-1110	0.9	2.5	740.0	822.2	296.0
	(0.32 ÷ 1.48)	(1.46 ÷ 3.54)	(676.0 ÷ 804.0)		
ADK-1100	0.34	0.30	81.00	238.2	270.0
	(0.19 ÷ 0.49)	(0.22 ÷ 0.38)	(76.90 ÷ 85.50)		
Cardiocyclide	0.27	0.24	40.0	148.1	167.0
	(0.21 ÷ 0.33)	(0.20 ÷ 0.28)	(35.5 ÷ 44.5)		
Lidocaine (Avduynina et al. 2019)	7.5	7.8	39.4	5.2	5.0
Verapamil (Avduynina et al. 2019)	1.1	–	17.0	15.4	
Ethmosine (Avduynina et al. 2019)	–	0.2	11.5	–	58.0
Novocainamide (Avduynina et al. 2019)	–	41.0	110.0	–	2.7

Note: the effective dose (ED_{50}) and lethal dose (LD_{50}) with confidence limits were calculated by the method of Miller and Tainter at a probability level of $p = 0.05$.

Table 2), the maximal action potential duration (APD_{70}), diastolic slope (dV/dt_4) among the sinus node pacemakers, and the smallest values of dV/dt_0 and action potential amplitude (APA).

2. Potential True Pacemakers (PTPs) (Fig. 1.B.2, Table 2) – a type of latent pacemakers which significantly differ from TPs: lower R_{4-0}, and higher dV/dt_0 values.

3. Transitional Latent Pacemakers (TLPs) (Fig. 1.B.3, Table 2) are mainly located in the periphery of the sinus node. They are distinguished from the first two types by higher dV/dt_0 values. However, the values of R_{4-0} and APD_{70} for TLPs were significantly lower than for PTPs.

4. Atrial Type Pacemakers (ATP) (Fig. 1.B.4, Table 2) are located on the border of the sinus node and the surrounding atrial working cardiomyocytes (AWC). It should be noted that dV/dt_4 in these cells is minimal among all pacemaker cells (4.5±0.7 mV/s), while the values of APA, dV/dt_0 and APD_{70} were almost indistinguishable from those in AWC (Fig. 1.B.5, Table 2).

Thus:

A. Amplitudes of action potentials (APA) of TP, PTP, and TLP subpopulations are similar. In ATP and AWC, the amplitudes of action potentials are much higher (Table 2).

B. The diastolic slope (dV/dt_4) in the subpopulations of TP, PTP and TLP, as in the previous case, is approximately equivalent. In ATP, this indicator is significantly lower.

C. R_{4-0} and APD_{70} fall in the order TP → PTP → TLP → ATP, and these indicators in ATP differ significantly from the indicators of the first three types.

D. And, finally, dV/dt_0 in the order TP → PTP → TLP → ATP → AWC naturally increases, which indicates an increase in the proportion of fast sodium channels ($Na_v1.5$ channels) in the sarcolemma of these types of cardiomyocytes. When studying true pacemakers using the patch clamp method, fast sodium current is not detected, which indicates the absence or inactivation of fast sodium channels in these cells (Satoh 2003; Dobrzynski et al. 2007).

From all of the above, it can be seen that TP, PTP, and TLP are a single functional group with basically similar electrophysiological characteristics. Electrophysiological characteristics of ATP stand alone.

Analysis of the effect of succinic acid ester of 5-hydroxyadamantan-2-one on rat heart pacemaker cells

The sinus node of the rat heart is technically a very complex object for working with the constituent cardiomyocytes using microelectrode techniques because:

- the diameter of the pacemaker cells in their widest part (and they have a fusiform shape) is only 37 micrometers (Sutiagin 2009);
- "soft" skeleton of the rat heart sinus node is represented by a collagen network, and the quantitative content of connective tissue in it reaches 70% (Pavlovich and Chervova 1983).

Thus, we had to thoroughly improve the "geometry" of the glass microelectrode tip to a state where it could pierce the dense connective tissue of the intercellular matrix, while remaining inside the cell without its visible damage. Naturally, the size of the cell implies the instant "fall" of the microelectrode out of the cell at the slightest mechanical impact.

During the experimental studies, 32 intracellular records lasting from 3 to 116 minutes were made. The average recording time was 43±28 minutes.

True Pacemakers

In total, 8 records with TP were obtained (4 – with a ADK-1110 concentration of 5 mg/L, 2 – with a concentration of 50 mg/L, and 2 – with sequential administration

Table 2. Initial Electrophysiological Cell Types Examined for the Effect of 5-hydroxyadamantan-2-one Succinic Acid Ester in Vitro

Pacemaker type	Quantity of cells	APA (mV)		dV/dt_0 (V/s)		dV/dt_4 (mV/s)		R_{4-0} (cu)		APD_{70} (ms)	
		Range	M±м	Range	M±м	Range	M±м	Range	M±м	Range	M±м
True Pacemaker (TP)	6	58.0–69.6	63.1±5.3	5.5–17.7	10.0±4.8	9.6–17.4	13.7±2.9	9.2–22.8	15.9±5.1	55.3–111.9	82.1±22.3
Potential True Pacemaker (PTP)	4	49.8–81.0	64.0±13.9	6.2–32.6	18.1±10.9	6.2–15.8	9.9±4.3	2.0–7.7	5.1±3.0	47.3–87.6	63.6±17.6
Transitional Latent Pacemaker (TLP)	10	48.3–77.8	64.6±8.6	10.3–61.4	27.9±17.9	4.7–16.9	10.2±3.7	1.2–4.4	2.4±1.1	35.9–53.8	46.7±5.7
Atrial Type Pacemaker (ATP)	4	73.1–89.8	81.8±8.4	49.6–119.7	79.8±33.4	3.8–5.4	4.5±0.7	1.0–2.1	1.6±0.6	26.8–43.0	34.4±6.7
Atrial Working Cardiomyocyte (AWC)	2	94.5–101.7	98.1±5.1	63.0–112.9	87.9±35.3					32.6–35.2	33.9±1.8

Note: Standard deviation was used as a statistical method

of 5 mg/L and 50 mg/L). The analysis of the electrical activity characteristics in three cases showed a decrease in APA and dV/dt_0 (5 mg/L). In all other cases, no significant changes in the characteristics of action potentials were observed.

Potential True Pacemakers

In total, 4 records with PTPs were obtained (3 – with a ADK-1110 concentration of 5 mg/L and 1 – with sequential administration of 5 mg/L and 50 mg/L). In three cases (even at 5 mg/L concentration), a decrease in dV/dt_0, an increase in dV/dt_4, and an increase in R_{4-0} were detected, i.e. transformation of action potentials of PTP into TP (Fig. 2.1.B). A subsequent increase in the concentration of succinic acid ester of 5-hydroxyadamantan-2-one to 50 mg/L did not cause further transformation of the action potentials (Fig. 2.1.C). In one case (5 mg/L), on the contrary, there was an increase in dV/dt_0, a decrease in dV/dt_4 and a decrease in R_{4-0}, i.e. conversion of PTPs to TLPs (Fig. 2.2).

Transitional Latent Pacemakers

In total, 12 recordings with TPs were obtained (5 – with a concentration ADK-1110 of 5 mg/L, 5 with – 50 mg/L, and 2 – with sequential administration of 5 mg/L and 50 mg/L). On the basis of changes in dV/dt_0, dV/dt_4 and R_{4-0} in 3 cases, the TLP action potentials were transformed into PTP action potentials (2 – with a concentration of 5 mg/L, in 1 case – 50 mg/L), in 2 cases – into the ATP potentials (one – with a concentration of 5 mg/L and one – 50 mg/L (Fig. 2.3)), and in the remaining seven cases, the TLP action potential remained unchanged.

Atrial Type Pacemakers

A total of 6 recordings with ATPs were obtained (4 – with a concentration ADK-1110 of 5 mg/L and 2 – with sequential administration of 5 mg/L and 50 mg/L). Despite changes in some characteristics, the action potentials of ATPs remained within the chosen type.

Atrial Working Cardiomyocytes

In total, 2 recordings with AWCs were obtained (1–5 mg/L and 1–50 mg/L). In both cases, the APA and dV/dt_0 decreased at the potentials of action of AWCs.

Thus, the effects of ADK-1110 on pacemakers of the rat heart sinus node should include:

1. The absence of significant changes in the characteristics of the initial True Pacemakers;
2. Expansion of the zone occupied by True Pacemakers, due to Potential True Pacemakers;
3. Expansion of the zone occupied by Potential True Pacemakers, due to the Transitional Latent Pacemakers;
4. The absence of fundamental changes in the electrophysiological characteristics of ATPs and AWCs.

It should also be noted that in two experiments, a complete stop of the rhythmic activity of the right atrial preparation (sinus arrest) was observed within the first minutes of administering succinic acid ester of 5-hydroxyadamantan-2-one solution into the flow-cell (on the 3rd and 9th minutes), this effect wearing off by washing the preparation with an intact Krebs-Ringer solution.

Discussion

The data that is shown in this article has been obtained for the first time and indicates a high antiarrhythmic activity of ADK-1110, which has low toxicity and was previously proposed as a compound with a cerebrovascular anti-ischemic activity (Kurza et al. 2018). The antiarrhythmic activity of the compound was studied on calcium chloride and aconitine models of arrhythmias in awake rats. When determining the antiarrhythmic index of ADK-1110 under the conditions of the calcium chloride model of arrhythmia, it turned out that the compound significantly exceeded the known reference drugs in terms of the antiarrhythmic index – class I (lidocaine), class IV (verapamil), and class III (cardiocyclide), according to

1

A

B

C

2

A

B

3

A

B
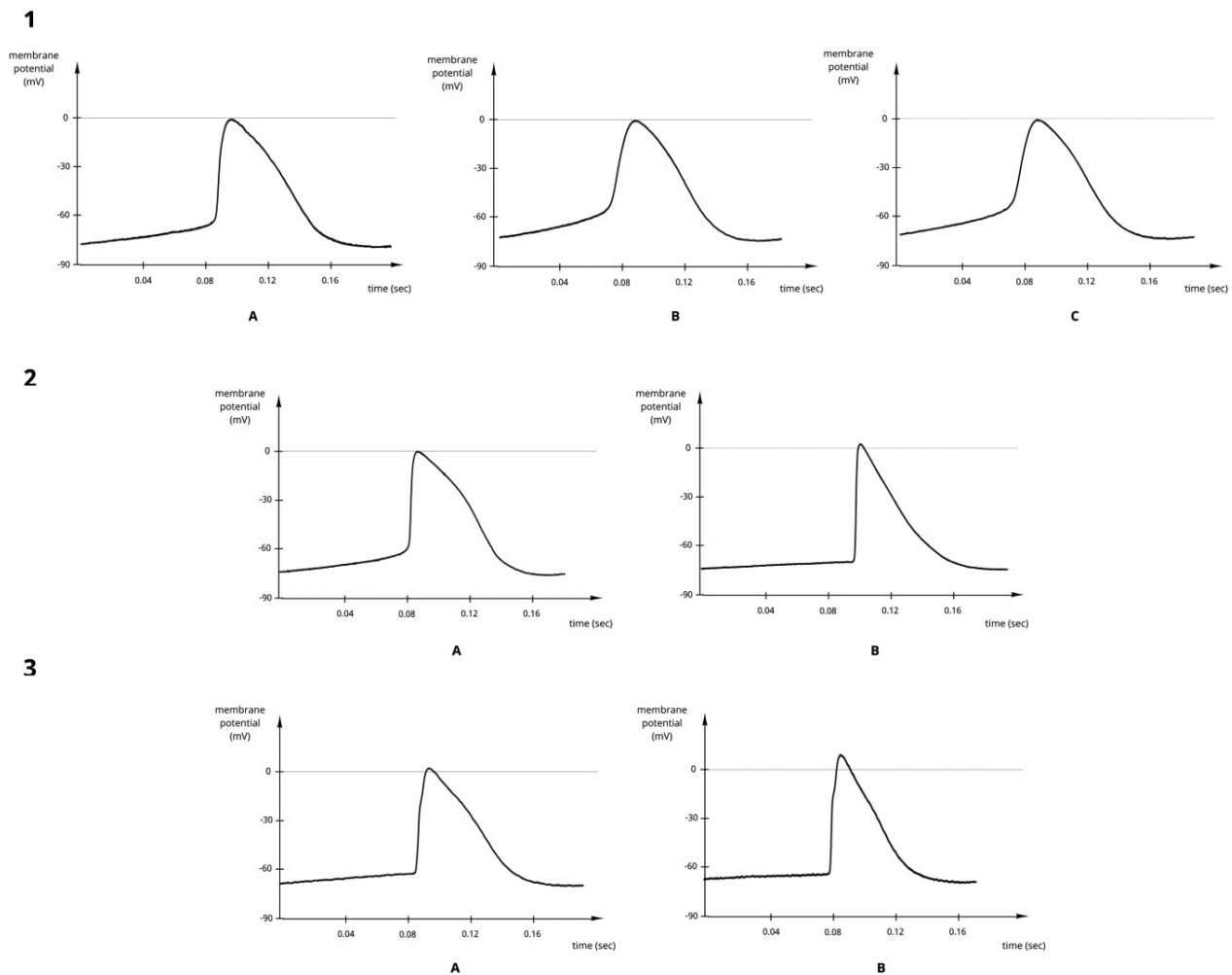
Figure 2. Transformation of PTP and TLP action potential under the influence of ADK-1110 in Krebs-Ringer solution. **Note: 1.** Transformation of the action potential of Potential True Pacemakers under the influence of ADK-1110 in Krebs-Ringer solution. **A.** Action potential of an intact Potential True Pacemaker; **B.** Action potential of the same Potential True Pacemaker as a result of exposure to a solution of ADK-1110 at a concentration of 5 mg/L; **C.** Action potential of the same Potential True Pacemaker as a result of sequential exposure to a solution of ADK-1110 at a concentration of 50 mg/L **2.** Transformation of the action potential of Potential True Pacemakers under the influence of ADK-1110 in Krebs-Ringer solution. **A.** Action potential of an intact Potential True Pacemaker; **B.** Action potential of the same Potential True Pacemaker as a result of exposure to a solution of ADK-1110 at a concentration of 5 mg/L. **3.** Transformation of the action potential of Transitional Latent Pacemakers under the influence of ADK-1110 in Krebs-Ringer solution. **A.** Action potential of an intact Transitional Latent Pacemaker; **B.** Action potential of the same Transitional Latent Pacemaker as a result of exposure to a solution of ADK-1110 at a concentration of 50 mg/L.

E. Vaughan-Williams, as well as the previously proposed adamantane derivative of ADK-1100 (Avdyunina et al. 2019). ADK-1110 significantly exceeds the comparison drugs – class I (ethmosine, lidocaine, novocainamide) and class III (cardiocyclide), and is not inferior to ADK-1100 in terms of the window of the therapeutic effect under the conditions of the aconitine model of arrhythmia.

Thus, the obtained data indicate the presence of the properties of antiarrhythmics of classes I, III, and IV in ADK-1110.

The study of the effect of ADK-1110 on rat sinus node pacemakers did not reveal significant changes in the characteristics of the initial True Pacemakers. However, in this case, the predominant transformation of the action potentials of Potential True Pacemakers towards True Pacemak-

ers and those of Transitional Latent Pacemakers towards Potential True Pacemakers was shown. Thus, the effect of ADK-1110 leads to an increase of the area occupied by True Pacemakers due to latent pacemakers of the peripheral part of the sinus node, which stabilizes the functionality of the sinus node in terms of maintaining normal sinus rhythm. It is important to note that this effect is not accompanied by a pacemaker shift (a change in the location of the leading group of pacemakers within the sinus node), which is extremely characteristic of all kinds of regulators of cardiac chronotropy when regulating the sinus node activity (Boyett et al. 2000; Sutyagin et al. 2009). Atrial Type Pacemakers lie on the border of the sinus node and the atrial working myocardium, the main function of which, according to the literature, is to restrain the hyperpolarizing effect

on the central part of the sinus node from the working atrial muscles (Boyett et al. 2000). ADK-1110 does not significantly affect their electrophysiological characteristics.

Unlike the well-known antiarrhythmic drug ethmosine, the antiarrhythmic effect of which, in particular, is to limit the conductivity of electrical excitation between working atrial cardiomyocytes (Abalakov et al. 2018), ADK-1110 only stabilizes the functional activity of the central part of the sinus node.

belonging to various chemical classes and pharmacological groups: ethmosine, lidocaine, novocainamide, verapamil, and cardiocyclide, as well as the adamantane derivative of ADK-1100. ADK-1110 also has a cerebrovascular anti-ischemic property. This combination can be useful and necessary both in the treatment of patients with cardiac arrhythmias, which are combined or complicated by cerebrovascular disorders, and patients with cerebrovascular disorders, which are accompanied by cardiac arrhythmias.

Conclusion

Thus, a new antiarrhythmic drug is proposed, which has a significant advantage over the known reference drugs

Conflict of interest

The authors have no conflict of interest to declare.

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