HEART RHYTHM DISORDERS AS A RESULT OF CHANGES IN IONIC CHANNELS

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The electrical activity of the heart under physiological conditions begins with the excitation of the cells of the sinoatrial (SA) node. Slow diastolic depolarization of SA node cells results in an action potential that propagates through the atria, atrioventricular (AV) node, His–Purkinje system, and ventricular myocardium, causing excitation. Thus, due to electromechanical coupling, sequential contraction of the atria and ventricles occurs. The action potential of cardiomyocytes consists of 5 successive phases: 1) the fast depolarization phase (phase 0) begins during the entry of Na + ions into the cell through fast sodium channels; 2) early rapid repolarization phase (phase 1);

2+ ions enter simultaneously through slow calcium channels and K + ions exit ; 4) phase of late rapid repolarization (phase 3), caused by the predominant release of K + ions ; 5) phase 4 – resting potential. The development and maintenance of action potentials in the myocardium are regulated by the functioning of a variety of ion channel proteins. Transmembrane proteins provide a constant flow of ions through ion channels to the sarcolemmas of cardiomyocytes, generating electrical impulses.

Ion channels are divided into voltage-, chemo- and mechanically-gated. All ion channels consist of main α subunits and accessory subunits. The main structure of the ion channel is the α subunits, which determine its normal function, and additional β subunits regulate only the kinetics of the channel. The correct organization of the electrical activity of the heart is achieved due to the normal functioning of the ion channels of cardiomyocytes. When genes encoding ion channel proteins are mutated, so-called channelopathies develop, manifested by life-threatening arrhythmias. The diversity of cardiac ion channels and their functions requires an integrated approach in the diagnosis and treatment of cardiac arrhythmias. Understanding the role of ionic currents in the formation of action potentials under physiological conditions and during pathological changes can contribute to the successful selection of antiarrhythmic drugs for the effective treatment of arrhythmias and their use with the minimum possible probability of arrhythmogenic action. In many cases, antiarrhythmic therapy is not

sufficient to effectively prevent sudden cardiac death due to life-threatening arrhythmias. This category of patients requires implantation of a cardioverter-defibrillator. The widespread introduction of genetic and cellular technologies in the future may solve the problems of prevention and treatment of congenital heart channelopathies.

Key words: ion channels; arrhythmias; cardiomyocytes.

Introduction

The electrical activity of the heart under physiological conditions begins with the excitation of the cells of the sinoatrial (SA) node. Slow diastolic depolarization of the SA node cells results in an action potential that propagates through the atria, the atrioventricular (AV) node, the His a–Purkinje system, and the ventricular myocardium, causing their excitation. Thus, due to electromechanical coupling, sequential contraction of the atria and ventricles occurs. Slow diastolic depolarization is characteristic of both the cells of the SA node and the cells of the AV node, His c a bundle and Purkinje fibers, however, this property manifests itself only when the SA node fails or is weak, since under normal conditions their spontaneous activity is suppressed more frequent impulses from the SA node (overdrive suppression). Slow diastolic depolarization is not typical for cells of the working myocardium due to the fact that at rest the intracellular potential of the cells has a negative value, which is due to the greater permeability of the cell membrane to K + ions [1].

The action potential of cardiomyocytes consists of 5 successive phases: 1) the fast depolarization phase (phase 0), begins when Na + ions enter the cell through fast sodium channels; 2) early rapid repolarization phase (phase 1); 3) the phase of slow depolarization, or plateau (phase 2), when Ca 2+ ions enter simultaneously through slow calcium channels and K + ions exit ; 4) phase of late rapid repolarization (phase 3), caused by the predominant release of K + ions ; 5) phase 4 – resting potential.

The development and maintenance of action potentials in the myocardium are regulated by the functioning of a variety of ion channel proteins. Transmembrane proteins provide a constant flow of ions through ion channels to the sarcolemmas of cardiomyocytes, generating electrical impulses. Each ion channel is a protein molecule located in the membrane of the cardiomyocyte. All ion channels are in one of three states at different times: resting, activation and inactivation. Due to the transition of ion channels from a resting state to an activation state, a current of ions occurs, forming a membrane current. There are about 100 thousand ion channels in the membrane of each cardiomyocyte. Most channels are selective and allow only one type of ion to pass through. Ion channels are divided into voltage-, chemo-, and mechanically controlled [2]. All ion channels consist of main α subunits and accessory subunits. The main structure of the ion channel is the α subunits, which determine its normal function, and additional β subunits regulate the kinetics of the channel. The correct organization of the electrical activity of the heart is achieved due to the normal functioning of the ion

channels of cardiomyocytes. When genes encoding ion channel proteins are mutated, so-called channelopathies develop, manifested by life-threatening arrhythmias. This article will review current data on the normal physiology and pathology of cardiomyocyte ion channels, as well as the accompanying life-threatening arrhythmias.

Incoming ion currents

Fast sodium current (INa)

INa occurs through voltage-gated Na + channels and provides rapid depolarization (phase 0) in ventricular and atrium cardiomyocytes and in Purkinje fiber cells. The voltage-gated Na + channel consists of one α -subunit and two β -subunits.

The main functions of the channel (sensitivity to the level of membrane potential, activation and inactivation) are associated with the α subunit. Currently, only one subfamily of α -subunits of Na channels is known – Nav1, in which 9 isoforms are distinguished. Of these, Nav1.5 is the only subunit expressed in human heart. Under normal physiological conditions, during the plateau phase of the cardiomyocyte action potential, approximately 99% of Nav channels are inactivated. Impaired Nav inactivation leads to the development of life-threatening cardiac arrhythmias [3].

The main α -subunit of the sodium channel that forms the Nav1.5 sodium current is encoded by the SCN5A gene. The mutation of this gene is associated with the development of such severe cardiac arrhythmias as congenital long QT syndrome (LQTS 3), sudden infant death syndrome, idiopathic ventricular fibrillation, sick sinus syndrome (type 2), Brugada syndrome (type 1). type), arrhythmogenic dysplasia of the right ventricle (type 5) and progressive conduction disorder, Leva-Lenegra disease. Thus, a mutation in the SCN5A gene, associated with the development of congenital long QT syndrome (LQTS 3), causes a defect in sodium channel inactivation, leading to the appearance of a late sodium current, absent normally, which neutralizes the outgoing K + current and prolongs the “plateau” , which leads to prolongation of the ventricular action potential (prolongation of the QT interval). In turn, prolongation of the QT interval increases the likelihood of early afterdepolarizations causing polymorphic ventricular tachycardia of the “ torsade” type de point 's " [4, 5]. Unlike LQTS 3, Brugada syndrome is characterized by a slowing of the depolarizing sodium current and, as a consequence, a slowing of the rate of rapid depolarization in the epicardium of the right ventricle. A decrease in the density of Na + channels relative to the density of the short-term outgoing current Ito leads to premature repolarization and shortening of the action potential in the epicardium, while in the endocardium depolarization of the inner layers of the membrane proceeds normally. In this regard, electrical heterogeneity of the right ventricular myocardium develops. As a consequence, the depolarized endocardium can become a source of repeated excitation of the prematurely repolarized epicardium, and the development of polymorphic ventricular tachycardia (VT) is possible [6, 7].

Leve-Lenegres syndrome is characterized by a progressive slowing of conduction throughout the conduction system of the heart without increasing the risk of developing life-threatening ventricular arrhythmias. In Leve–Lenegres syndrome, activation of the Na + channel requires exposure to a suprathreshold stimulus [8]. The morphological substrate of this syndrome is progressive sclerodegenerative damage to the conduction system of the heart. On the ECG, this syndrome can be represented by a combination of complete block of the right bundle branch and block of the anterosuperior branch of the left bundle branch [9].

QT syndrome (LQTS4) is a consequence of a mutation in the gene encoding ankyrin B. Ankyrin B is part of a group of multifunctional adapter membrane proteins involved in the regulation of the Na + channel. LQTS 4 is the least studied of all types of LQTS [10].

Calcium currents (ICa, L and ICa, T)

2+ currents were found in cardiomyocytes : L- and T-type. Ca 2+ channels of heart cells consist of the main subunit α 1 and auxiliary subunits α 2d and □□2. L-type ICa is more represented in ventricular cardiomyocytes compared to atrial cardiomyocytes. In the cells of the SA and AV node, ICa L-type spontaneous depolarization and impulse conduction are formed.

These channels are formed from α 1-subunits of the Cav1.x family. Of these, Cav1.2 (α1C) and Cav1.3 (α1D) isoforms are found in the heart. L-type ICa are inhibited by calcium antagonists such as verapamil, nifedipine, and diltiazem [11].

T-type ICa are most abundant in pacemaker cells and the conduction system of the heart. The amplitude of the T-type ICa current is 20% of the amplitude of the L-type ICa current. They consist of α 1-subunits of the Cav3.x family; isoforms Cav3.1 (a1G) and Cav3.2 (α 1H) are found in the heart. Unlike L-type ICa, they are not sensitive to intracellular Ca 2+ concentrations and are not blocked by classical calcium channel antagonists.

A significant role in maintaining intracellular homeostasis of Ca 2+ ions belongs to ryanodine receptors RyR2. Violation of their function leads to excessive release of Ca 2+ from the sarcoplasmic reticulum, causing Ca 2+ overload and increasing the triggering activity of the ventricular myocardium.

The rhyanodine receptor is the main structure of calcium channels in the sarcoplasmic reticulum of cardiomyocytes [8]. The fundamental role of ryanodine receptors is to activate voltage-gated calcium channels in the plasmalemma. N. Liu et al. first revealed that dysfunction of ryanodine receptors (RyR2) is the cause of the development of catecholaminergic polymorphic ventricular tachycardia. The result of mutations in the RyR2 gene is the development of about 55% of cases of catecholaminergic polymorphic ventricular tachycardia [12].

The second genotype of catecholaminergic polymorphic ventricular tachycardia (CVPT2) is associated with mutations in the calsequestrin-2 (CASQ2) gene, mapped

on chromosome 1 at the 1p13.3–p11 locus. Calsequestrin-2 is the main calcium-binding protein in the sarcoplasmic reticulum of cardiomyocytes.

The RyR2 and CASQ2 proteins are involved in the same intracellular metabolic process associated with the control of intracellular calcium fluxes and the concentration of free calcium in the cytoplasm. Due to mutations in both genes, there is an increased release of calcium ions from the sarcoplasmic reticulum in response to the entry of calcium ions into the cell, causing an overload of cells with these ions, which enhances the transmembrane dispersion of repolarization and triggers VT by the reentry mechanism [11].

Pacemaker current (If)

If is an incoming non-selective Na + - and K + - current, which is activated by hyperpolarization of the membranes of pacemaker cells. If in pacemaker cells of the SA node occurs during the repolarization phase of the action potential and makes a major contribution to slow diastolic depolarization (SDD) of pacemaker cells. If passes through channels formed by subunits of the HCN family.

Currently, 4 isoforms of HCN are known, HCN1–HCN4, of which HCN1, HCN2 and HCN4 are expressed in the heart. In the SA node and Purkinje system, the expression of HCN4 is more pronounced and HCN1 and HCN2 are less expressed. The effect of acetylcholine and beta-adrenergic agonists on If occurs through changes in the activity of the enzyme adenylate cyclase and the production of cyclic adenosine monophosphate (cAMP). The effect of cAMP on If is due to direct interaction with the channel through which this current flows. A decrease in the function of If channels can cause the development of sick sinus syndrome [9].

Outgoing currents

Short-term output current (Ito)

Ito is involved in the early repolarization phase of the action potential of cardiomyocytes and cells of the His–Purkinje conduction system. Ito consists of the voltage-sensitive, Ca 2+ -independent K + -current Ito1 and the calcium-activated Cl - current Ito2.

Ito1 is found in the atria and ventricles of many animal species, as well as in the rabbit SA node. This selective K + -current is rapidly activated and inactivated, it is not sensitive to Ca 2+ , and is blocked by 4-aminopyridine.

Ito2 is involved in the early repolarization phase together with Ito1. During Ca 2+ overload, Ito2 may contribute to the arrhythmogenic Iti current involved in triggering activity. Ito2 is suppressed by the ion transport inhibitors DIDS, SITS and niflumic acid [13].

Delayed rectification current (IC)

IK is so called due to its relatively slow activation compared to other currents. Three components of IK are known – IKs, IKr and IKur, which differ in temporal kinetics and pharmacological sensitivity [14].

IKs (slow IK) is activated quite slowly (in 800 ms at 0 mV), blocked by chromanol 293B and L-735821. IKs flows through 4.5 pS channels that are formed from the KvLQT1 subunit and an additional minK.

IKr (fast IC) activates relatively quickly (within 200 ms at a potential of 0 mV). IKr is blocked by class III antiarrhythmic drugs. The conductivity of the channels through which IKr flows is 2 pS. The channel molecule consists of the main subunit HERG and an additional MiRP1.

IKur (ultrafast IC) activates very quickly (within 10 ms at 0 mV) and inactivates very quickly. The channels through which the IKur current flows are formed from Kv1.5 subunits.

All three IK components play a major role in repolarization at the end of phases 2 and 3 of the cardiomyocyte action potential. It is worth noting that due to different rates of inactivation, their contribution to repolarization directly depends on heart rate. An increase in IKs with an increase in heart rate leads to an acceleration of repolarization and, therefore, a shortening of the action potential (so-called “frequency adaptation”). Reducing the duration of the action potential leads to a decrease in the degree of activation of IKr. Together with an increase in the amplitude of IKs, this ensures an increased role of IKs in the repolarization of cardiomyocytes. This change in currents underlies the frequency dependence of the action of selective K + channel blockers. IKr and IKs, due to their slow inactivation, may play an important role in the formation of DMD of SA node pacemaker cells. The different duration of the action potential in cardiomyocytes of different parts of the heart is due to the unequal level of expression of the channels through which IKur, IKr and IKs flow. The shorter action potential in the atria is due to the presence in them of a large amount of IKur, which is absent in the ventricles. Also, the amplitude of IKr is much greater in the left atrium than in the right atrium, resulting in the action potential in the left atrium being relatively shorter. In the ventricles, IKr is expressed to a greater extent in epicardial and apical cardiomyocytes, where the action potential is also shorter. The rather long action potential duration in ventricular M cells is a consequence of the low amplitude of IKs. The important role of IK in the repolarization of cardiac cells is confirmed by a number of congenital and acquired forms of long QT interval syndrome , which are caused by dysfunction of these channels.

Thus, two mutations of the gene encoding the α -subunit of IKs are the causes of two congenital syndromes: LQTS1 and LQTS-JLN1 (1st form of Jervell and Lange-Nielsen syndrome). And two mutations in the gene for the β -subunit (MinK) of IKs cause the syndromes LQTS5 and LQT-JLN2 [14].

Mutation of the α subunit of IKr (HERG) causes the development of LQTS2 syndrome, and mutation of the β subunit (MiRP1) of the same channel leads to LQTS6 syndrome [15].

All of these syndromes are united by prolongation of the QT interval , which becomes a substrate for the development of life-threatening ventricular tachycardia.

the QT interval causes mutations in potassium channel genes, leading to increased IKr activity, shortening the duration of the repolarization phase of the action potential and reducing the duration of the refractory period of the ventricular myocardium, which is accompanied by a decrease in the excitation wavelength, predisposing to the occurrence of ventricular arrhythmias by the reentry mechanism.

Abnormal current (incoming)

rectification (IK1)

IK1 is located in Purkinje fibers, atrial and ventricular cardiomyocytes. IK1 is called anomalous (input) rectification due to the fact that the channels that carry its current are activated only at negative potentials and more often conduct incoming current than outgoing current. IK1 is involved in repolarization and maintenance of the resting potential of cells. At positive potentials, IK1 is inactivated.

Mutations in the gene encoding the IK1 channel (Kir2.1) lead to the development of LQTS7 (Andersen–Tawil syndrome) [11, 16]. Disruption of the function of the Kir2.1 protein leads to an extension of the 3rd phase of repolarization, and the action potential of cardiomyocytes accordingly lengthens. In turn, prolongation of the action potential causes calcium overload, activates the inward sodium-calcium exchange current (INa/Ca), which causes early phase 3 depolarization and prolongs the subsequent phase 4 depolarization, leading to ventricular tachycardia [17].

Acetylcholine-activated K + -current IK (ACh)

IK (ACh) is most found in pacemaker and atrial cells and Purkinje fibers. Activation of the channels through which IK (ACh) flows occurs due to the action of acetylcholine on M2 cholinergic receptors of cardiomyocytes. Activation of IK (ACh) causes hyperpolarization and significant shortening of the action potential duration of pacemaker and atrial cells. In addition, activation of IK (ACh) plays an important role in the negative chronotropic effects of acetylcholine. IK (ACh) is potential sensitive, characterized by abnormal (incoming) rectification, due to which it plays a major role at potentials close to the resting potential, and is practically absent during the depolarization phase and plateau of the action potential [18].

ATP-sensitive K + -current IK (ATP)

IK (ATP) mediates the connection between cardiac metabolism and its electrical activity. IK (ATP) is suppressed by intracellular ATP. More precisely, extracellular ATP inhibits IK (ATP) at micromolar concentrations, and intracellular ATP at millimolar concentrations. Therefore, under physiological conditions, IK (ATP) is inactivated. If intracellular ATP concentration decreases due to ischemia or hypoxia, IK (ATP) is activated, leading to shortened action potentials and the development of life-threatening ventricular arrhythmias [19].

Mechanically dependent ion currents

It is known that the electrophysiological parameters of the heart change when it is stretched. Such changes are associated with ionic currents flowing through specialized stretch-activated channels (SAC) ion channels. Most SACs are nonselective, meaning they allow Ca 2+ , Na + , and K + ions to pass equally , while other channels are selective for certain ions. The presence of inward and outward currents (ISAC) flowing through the SAC explains the various mechanisms by which stretch affects cardiac electrophysiological parameters. Thus, activation of outgoing ISACs accelerates repolarization during the plateau phase, which leads to a shortening of the duration of the action potential and, as a consequence, the effective refractory period. The most studied molecular structure is K + SAC, which consists of TREK-1 subunits. These channels are activated by mechanical stretching, as well as

under the action of arachidonic acid.

Ion pumps

In cardiomyocytes and pacemaker cells, in addition to ion channels, ion pumps and exchangers play a special role in the formation of the action potential. They ensure the maintenance of a constant intracellular level of K + , Na + and Ca 2+ ions . The INa/K pump provides active transport of Na + and K + ions across the cell membrane. The INa/K pump is a P-type ATPase and consists of α and β subunits. Four isoforms of α- and β -subunits have been identified, which in any combination produce a working pump. The INa/K pump can lead to hyperpolarization, shortened action potential duration, and slower spontaneous activity. The operation of the INa/K pump depends on the intracellular Na + concentration . The INa/K pump is inhibited by cardiac glycosides, in particular digitalis.

The Na/Ca exchange current is formed due to the operation of the electrogenic Na + /Ca 2+ exchange mechanism, during one cycle of operation of which 3 Na + ions per 1 Ca 2+ ion enter the cell through the cell membrane . The direction of INa/Ca depends on the ratio between Na + - and Ca 2+ gradients and the membrane potential. During phase 4 of the action potential, the Na/Ca exchange generates a small inward current. After rapid depolarization (phase 0), INa/Ca may be outgoing for a short time, then becomes inward as the intracellular Ca 2+ concentration increases. Thus, INa/Ca is involved in the formation of the plateau (phase 2) of the action potential in cardiomyocytes and ensures the release of Ca 2+ ions from the cells. Suppression of INa/Ca leads to a shortening of the duration of the action potential. INa/Ca may also play an important role in the formation of DMD in pacemaker cells.

The work of the Na + /Ca 2+ exchanger is regulated by pH, □□-adrenergic stimulation. The role of Na/Ca metabolism in the development of electrophysiological disorders of cardiomyocytes is well represented during myocardial ischemia and reperfusion. Acidosis that occurs during ischemia leads, through suppression of the Na/Ca exchange function, to an increase in the intracellular concentration of Na + . During reperfusion, the pH of the cells outside is rapidly restored and a pH gradient

appears, which is compensated by Na + /H + exchange. At the same time, the intracellular Na + concentration increases , the Na + gradient and the work of the Na/Ca exchange mechanism decrease , which leads to an overload of cardiomyocytes with Ca 2+ ions . Overload of cardiomyocytes with Ca 2+ ions predisposes to the occurrence of late afterdepolarizations and, consequently, ventricular arrhythmias. Thus, suppression of the reverse operation of the Na/Ca exchange mechanism is a target for the prevention and treatment of reperfusion arrhythmias. Approximately the same disorders occur in heart failure. Thus, in heart failure, the level of expression of the Na/Ca exchange mechanism increases and the level of Ca 2+ ATPase in the sarcoplasmic reticulum decreases. A decrease in the level of Ca 2+ ATPase in the sarcoplasmic reticulum leads to an overload of cardiomyocytes with Ca 2+ ions with the subsequent development of ventricular arrhythmias.

Conclusion

Genetically determined dysfunction of ion channels or regulatory proteins can lead to the development of complex cardiac arrhythmias. The diversity of cardiac ion channels and their functions requires an integrated approach in the diagnosis and treatment of cardiac arrhythmias. Understanding the role of ionic currents in the formation of action potentials under physiological conditions and during pathological changes can contribute to the successful selection of antiarrhythmic drugs for the effective treatment of arrhythmias and their use with the minimum possible probability of arrhythmogenic action. In many cases, antiarrhythmic therapy is not sufficient to effectively prevent sudden cardiac death due to life-threatening arrhythmias. This category of patients requires implantation of a cardioverter-defibrillator. The widespread introduction of genetic and cellular technologies in the future may solve the problems of prevention and treatment of congenital heart channelopathies.

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