

## Mini-Review

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# New progress in understanding the cellular mechanisms of anti-arrhythmic drugs

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**Abstract:** Antiarrhythmic drugs are widely used, however, their efficacy is moderate and they can have serious side effects. Even if catheter ablation is effective for the treatment of atrial fibrillation and ventricular tachycardia, antiarrhythmic drugs are still important tools for the treatment of arrhythmia. Despite efforts, the development of antiarrhythmic drugs is still slow due to the limited understanding of the role of various ionic currents. This review summarizes the new targets and mechanisms of antiarrhythmic drugs.

**Keywords:** Antiarrhythmic drugs; New targets; Mechanism

## 1 Introduction

Arrhythmia is a common and dangerous cardiovascular disease [1]. Research and development of anti-arrhythmic drugs has been ongoing, however, there has been no obvious breakthrough in the past 20 years. In recent years, radiofrequency ablation and implantable cardioverter defibrillators (ICDs) have been widely used in clinical practice [2, 3]. The importance of anti-arrhythmic drugs in the treatment of arrhythmias has decreased significantly, and the scope of their applications has gradually narrowed. However, it is undeniable that anti-arrhythmic drugs still occupy a certain position in the treatment of arrhythmia. For the following reasons: most of acute episodes of

arrhythmia still require drugs to terminate the episode; some symptomatic supraventricular and ventricular premature beats need to be controlled with drugs and to prevent recurrence. In addition, some patients cannot be placed on ICDs or have radiofrequency ablation performed due to economic limitation. To enable clinicians and pharmacists to rationally evaluate antiarrhythmic drugs, various antiarrhythmic drugs are briefly discussed. Furthermore, we reviewed emerging antiarrhythmic drugs currently undergoing clinical investigation or already approved for clinical use.

## 2 Classification of anti-arrhythmic drugs

According to the electrophysiology and mechanism of action of Purkinje fiber in vitro, antiarrhythmic drugs can generally be divided into four categories: Class I sodium channel blockers, including three subclasses of A, B, C. Type IA is a modest blockade of sodium channels, representing drugs such as quinidine [4]; Type IB is a mild blockade of sodium channels, representing drugs such as lidocaine [5]; Type IC is a significant blockade of sodium channels, representing drugs such as flecainide [6]. Class II are beta-adrenoceptor blockers, representing drugs such as propranolol [7]. Class III are drugs that selectively extend the repolarization process; they prolong APD and ERP, representing drugs such as amiodarone [8]. Class IV are calcium antagonists, representing drugs such as verapamil [9]. According to recent research, there are two classification methods for class III antiarrhythmic drugs, which are classified according to the different types of potassium current blockage, drug development and clinical application. Based on the mechanism of potassium current blockage, they are divided into: (1) simple IKr blockers, representing drugs such as sotalol [10] and almokalant [11]; (2) simple IKs blockers, such as the compounds HMR-1556 [12] and L-768673 [13]; (3) complex type III anti-arrhythmic drugs. These drugs can be divided into 4 categories according to whether or

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not other ion channels are also blocked: without calcium blocking effect class, such as tedisamil; with calcium channel block type, such as azimilide and amiodarone;  $\beta$  receptor blockers, such as sotalol and amiodarone;  $\alpha$  receptor blockers, such as amiodarone etc.

### 3 Mechanism of action of antiarrhythmic drugs

Class I antiarrhythmic drugs block the fast sodium channels of myocardial cells, inhibit the influx of sodium in phase 4, reduce autoregulation, and slow down phase 0 depolarization [14]. Among them, class IA drugs also significantly prolong the repolarization process (APD, DRP). And to a certain extent, class IA drugs inhibit the permeability of  $K^+$  and  $Ca^{2+}$ , and thus have membrane stabilization effects. Therefore, class IA drugs have better effects on supraventricular arrhythmia [15]. The effect of class IB drugs on  $Na^+$  influx is weak, and has less influence on conduction. IB drugs can promote the outflow of  $K^+$ , shorten the repolarization process, and reduce the APD. IB drugs have a good effect on ventricular arrhythmias [16]. Class IC drugs have an obvious inhibitory effect on influx of  $Na^+$ , heavier inhibition of 0 phase depolarization and stronger effects on ventricular arrhythmia [17].

Class II antiarrhythmic drugs block the heart's  $\beta$  receptor, counteracting the effect of catecholamines on the heart. Class II antiarrhythmic drugs reduce autonomy of the sinus node, atrioventricular node, and conduction tissue, so that conduction is slowed, extending action potential duration and effectiveness of application period [18]. In recent years, it has been found that after sympathetic overexcitation, catecholamine binds to the  $\beta$ -receptor of the myocardial cell membrane, then a series of enzymatic actions can alter the configuration of  $Ca^{2+}$ ,  $Na^+$ , and  $K^+$  ion channels involved in phosphorylation [19]. These channels change, resulting in increased  $Ca^{2+}$  influx, and enhanced  $K^+$  outflow, which can cause the following detrimental results: (1) ventricular self-discipline increased and the formation of abnormal autoregulation; (2) refractory period shortened and conductive changes promote the formation of reentrant arrhythmias; (3) ventricular fibrillation reduced. Afterwards the  $\beta$ -receptor blockers can reverse the adverse effects of sympathetic nerve stimulation on the ion channels. Therefore,  $\beta$  receptor blockers have anti-arrhythmic effects in class I, II, III, and IV drugs [20].

Class III antiarrhythmic drugs mainly prolong the action potential duration and effective refractory period of atrial muscle, ventricular muscle and conduction tissue,

and have no obvious effect on self-discipline. According to recent studies, regardless of the type III antiarrhythmic drug, their common pharmacological mechanisms are specifically delayed rectifier potassium currents, including rapid activation of potassium current (IKr), slow activation of potassium current (IKs), prolongation of myocardial action potential time (APD) and effective refractory period (ERP), therefore causing anti-fibrillation [21].

Class IV antiarrhythmic drugs block slow cardiac calcium channels, inhibit extracellular calcium influx, slow the conduction of the atrioventricular node, and eliminate the atrioventricular nodal reentrant excitation [22].

### 4 New targets for antiarrhythmic drugs

The excitation of the myocardium is due to the instantaneous opening of sodium channels and the influx of sodium ions, which increases intracellular positive ions. Depolarization activates other channels on the membrane, such as potassium channels, Ito, IKr, IKs and IK1 are activated successively, the positive K ion is expelled, and the myocardial potential gradually tends to balance. The time of the repolarization can be expressed by APD. Due to the change of heart rate, the normal corrected QT value (QTc) is between 320~460 ms. QT reflects the normal length of myocardial repolarization. Over 460 ms is called long QT disease (LQTS) [23], shorter than 320ms is short QT disease (SQTS) [24]. Mutations in genes related to potassium and sodium channels on the myocardial membrane will lead to LQTS. The gene mutation that causes LQTS is mainly the IKs and IKr channel of potassium channel. IKs channel is composed of KCNQ1 (LQT1-KvLQT1, IKs $\alpha$  subunit) and KCNE1 (LQT5, HMIN, IKs $\beta$  subunit); and IKr channel is composed of KCNH2 (LQT2, HERG IKr) and KCNE2 (LQT6, IKr subunit). Sodium channels were constructed from SCN5A (LQT3, INa). LQT1 and LQT2 of potassium channel mutations were the most common. Gene mutations cause IKr (IKs) inactivation, APD extension, so that a rapid arrhythmia is formed by the non-reentrant mechanism.

Mutations of the potassium channel often result in the loss of function. However, the potassium channels IKr (KCNH2), IKs (KCNQ1), and IK1 (KCNJ2) can also incur gain-of-function mutations. KCNH2 mutations have many sites, and the cavitation site of the ion channel is particularly important [25]. The mutations that make up the cavitation site are particularly severe. The age segment

of sudden cardiac death is younger and the incidence is higher. The ion flow on the myocardial membrane is the basic component of myocardial repolarization. Their increase and decrease have great influence on the repolarization process and are the basic components of cardiac repolarization. Gene mutations reduce the outward ion flow and slow the repolarization, such as KCNQ1 and KCNH2 functional inactivation mutations., IKr or IKs becomes downregulated, APD is prolonged, constituting the activation mechanism of rapid ventricular arrhythmia [26]. Functional gain-of-function mutations of KCNQ1 or KCNH2 enhance the outward flow of ions (IKr, IKs), which accelerates the repolarization process. APD shortens the basis for the formation of impulsive reentry in the myocardium, which has a tendency to induce arrhythmias. For a long time, the relationship between the length of repolarization process and arrhythmia was not clear, and it was thought that prolonging APD is equivalent to antiarrhythmic activity. On the contrary, there is a significant correlation between drug prolongation of APD and Tdp. Tdp occurs in whole animals or humans, making them easier to develop into VFs. Therefore, the structural ion flow in the myocardium, especially IKr, cannot be obviously inhibited. Structural ionic currents are not involved in arrhythmia, but are closely related to arrhythmogenic.

Calcium channel gene mutations weaken inactivation, increase the inward ion current, delay the repolarization process, and prolong the APD, forming LQTS [27]. This mutation occurs in a variety of tissues, which slows the development of the nervous system and cause malformations. Induced potassium currents or calcium currents appear in myocardial lesions, which cause a strong arrhythmogenic tendency. Controlling induced currents will help control arrhythmias.

Arrhythmia occurs in the diseased heart. In addition to the marked changes of the ion channels on the membrane, there are also important changes in the intracellular calcium regulatory proteins in the sarcoplasmic reticulum. The intracellular sarcoplasmic reticulum RyR2 (Ryanodine receptor type 2) is an intracellular calcium release channel that responds to intracellular calcium release from the calcium influx of the I<sub>Ca</sub> L channel, and the excitatory coupling of calcium leads to contraction and relaxation of the cardiac cycle. The stable release of calcium from RyR2 (closed during diastole in the heart muscle) is maintained by the FKBP12.6 protein, which is an important biomarker associated with arrhythmia and heart failure.

If the  $\beta$  receptor is over activated, cAMP increases and produces excessive PKA, and it forms an over-phosphorylated state of RyR2. FKBP12.6 then dissociates

from the RyR2 macromolecule and is released into the cytoplasm. Once RyR2 is in the unstable state, the calcium release channel cannot be closed during the diastolic phase and a small amount of calcium flows out to form calcium leakage [28]. After dissociation, FKBP12.6 is no longer bound to RyR2 and dissociates in the cytoplasm. Free FKBP12.6 has been used as an important target for drug treatment of sudden cardiac death. Drug therapy has been shown to up-regulate FKBP12.6, causing it to recombine with RyR2 and thus stabilizing calcium release, which has become an important indicator for the treatment of arrhythmia and heart failure [29]. RyR2 gene mutations make RyR2 prone to FKBP12.6 dissociation tendency when phosphorylated. Therefore, patients with RyR2 mutations are prone to catecholaminergic polymorphic ventricular tachycardia (CPVT) during strenuous exercise, which is a common cause of sudden cardiac death in exercise [30]. The mutation rate of RyR2 is as high as 20%. The mortality rate of CPVT RyR2 mutation patients was 40% within 10 years after diagnosis [31]. Arrhythmogenic right ventricular cardiomyopathy is also associated with RyR2 mutation. Right ventricular myocardium shows steatosis and fibrous tissue lesions, and is prone to serious lethal arrhythmias. The I<sub>Ca</sub>L channel in the transverse tube controls the calcium influx, which is directed to the calcium release channel RyR2 in the cytoplasm, and a small amount of calcium inflows into RyR2 to release calcium from the sarcoplasmic reticulum, and is regulated by the calcium stable protein FKBP12.6. The released calcium is ingested by SERCA2a, which is regulated by phosphoprotein PLB. Therefore, the biological significance of calcium leakage is like an enhanced calcium influx, which has obvious arrhythmogenic properties. Down regulated FKBP12.6 is an important biomarker of arrhythmia. At the same time, SERCA2a and PLB are also downregulated. RyR2 and FKBP12.6 are down-regulated, reflecting the phenomenon of excessive activation of  $\beta$ -receptors, and only providing the underlying lesions that cause severe arrhythmias, which constitute what we refer to as ion channel disease in the resting state [32]. When there is stress and other activating factors, it may worsen the deterioration further and cause malignant arrhythmia.

The mechanism underlying the formation of malignant arrhythmia is very complicated, Therefore, the pathological changes of the myocardium are primary. It results in the upstream regulation of related ion channels. The phosphorylation of the corresponding target protein by PKA or PKC changes the biological activity. The regulation of gene transcription in the nucleus has abnormal up- or down-regulation. It has been reported that ACEI,  $\beta$ -blockers, carvedilol [33], and statin can all

improve the upstream pathological changes of myocardial ion channels and have a certain effect on prevention of severe arrhythmia. Conversely, the traditional drugs that block ion channels, such as IKr blocking drugs, [34] are ineffective. Therefore, the effectiveness of non-channel drugs has been valued.

## 5 Conclusions

Although the efficacy of antiarrhythmic drugs is moderate and side effects are worrisome, they are still an important part of treatment of patients with atrial and ventricular arrhythmias. The development of antiarrhythmic drugs has been slow, partly because we know little about the cellular mechanisms of arrhythmia. The next frontier of antiarrhythmic compounds will focus on new atrial dominant ion channels. The exploration of drug synergy will also become an important area of research in this field.

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