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Review

Vulnerable substrate and multiple ion channel disorder in a diseased heart will be new targets for antiarrhythmic therapy

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KEY WORDS anti-arrhythmic agents; myocardial infarction; hypertrophy; norepinephrine; levothyroxin; ion channels; CPU-86017

ABSTRACT

Life-threatening arrhythmia remains a problem contributing to major death in cardiovascular diseases. Till date the antiarrhythmic drugs (AAD) including the Class Ⅰ and the pure Class Ⅲ agents have not been recommended for controlling malignant ventricular arrhythmias in a diseased heart, not because of low efficacy but because of an increase in mortality due to their toxic effects. A vulnerable substrate (VS) possessing some properties such as reduced NE and SOD activity, hypertrophied myocardium, and an increase in QT dispersion, is reported to develop in non-infarcted zone of an infarcted heart. Hypertrophied ventricle and exaggerated cardiac arrhythmia can be produced on chronic medication with levothyroxin and this model shares some properties of VS. There is a significant difference in the pattern of disordered ion channels between the congenital long QT syndrome(LQTS) and the acquired heart disease. The affected ion channel in congenital LQTS is single. A novel mutation causing an early appearance of stop codon was discovered in HERG gene resultant with a single disarranged I_{Kr} channel leading to a prolonged QT interval. In contrast it is characterised with multi-channels and nonspecific disorder in the hypertrophied myocardium in the acquired heart disease. The disordered ion channel is the consequence of the VS lesion influencing the lipid membrane in a diseased heart. The VS and multiple ion channel disorder are provided as new targets to treat cardiac arrhythmias in a diseased heart.

INTRODUCTION

An infarcted heart is vulnerable to develop malignant cardiac arrhythmias finally degenerating into sudden cardiac death by ventricular fibrillation (VF)[1], possibly due to an existence of a vulnerable substrate (VS) in the diseased heart[2]. The life-threatening arrhythmia markedly contributes to the mortality in cardiovascular diseases, which remain a big problem in clinical treatment[3].

The pharmacological interventions to prevent acute myocardial infarction (AMI) and the chronic infarcted heart, have been focused on using antiarrhythmic drugs (AAD) with definite ion channel blocking action. A CAST (Cardiac Arrhythmias Suppressing Trial)[4] was conducted in 1,455 patients for 300 d to test the effectiveness of sodium channel blocking agents (the I_C group) in suppressing malignant arrhythmias in the post-infarcted patients and the outcome was discouraging due to a high mortality rate of, 4.5 % (33 of n = 730) of flecainide/encainide over placebo 1.2 % (9 of n = 725)[3]. The famous Sicilian gambit[5,6], thereafter, set up some theoretical considerations and the development of new AAD was shifted from the sodium channel blocking agents to a novel class, the pure Class Ⅲ[7,8] which possesses highly selective I_{Kr} blockade. The pure Class Ⅲ agents prolong the APD significantly without affecting other ion channels and β-receptors. Dextro-sotalol, which is devoid of the β-blocking action, and is recognized as an ideal AAD, was administered to test its ability to prevent post-infarcted patients from cardiac death. It was known as the SWORD (Survival with oral

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d-Sotalol)[8] trial in 3121 patients medicated for 18 months, which also unexpectedly ended to announce a high mortality 5.0 % (*d*-sotalol) over 3.1 % in placebo group[3]. It is as if people are coming to a maze and do not know where to go thereafter for the development of anti-arrhythmic agents[3,8-9].

In treatment of malignant ventricular arrhythmias in the clinical settings, the I_A and I_C subgroups of AAD and the pure Class Ⅲ agents result in no improvement in mortality, but an increase in mortality due to the toxic effects is observed. This the pure Class Ⅲ agents causing a higher rate of *torsade de pointes*, and the Class Ⅰ agents (particularly the I_A and I_C) are not recommended to control ventricular arrhythmias in a diseased heart. In patients with AMI the application of lidocaine (I_B group) could induce a suppression in arrhythmias but had no impact on the mortality. In a Multicenter Automatic Defibrillator Implantation Trail (MADIT) selective patients at a high risk of severe cardiac arrhythmias were treated to compare the therapeutic outcome between the AAD and the Implantable Cardioventer-defibrillator (ICD). The trial was stopped at 27 months of mean follow-up, because of an excessive mortality of 39 deaths (17 from cardiac causes) in the AAD group, versus 15 (11 from cardiac causes) in the ICD group ($P < 0.05$). So, the ventricular ICD[10] possibly including the radiofrequency ablation[9] are adopted as an alternate way to stop life threatening ventricular tachycardia. In a trial of Antiarrhythmic Versus Implantable Defibrillator (AVID) amiodarone was compared with ICD therapy in 1200 patients. During a follow-up lasting 2 – 3 years the study was interrupted in April 1997 because of a higher mortality in amiodarone group, 25 % higher mortality rate over the ICD group. In the clinical trials, the outcome of amiodarone varied, showing either reverse, neutral, or beneficial effects in treating ventricular arrhythmias in the diseased hearts. However, the β-blockers always showed a mild benefit of resulting in less mortality as compaired with the placebo[3,8].

The main clinical problem of the effectiveness and negative impact of mortality in AAD is in patients with either an infarcted or a diseased heart. The problem is attributed likely to the unawareness of the mechanism underlying the VS in an infarcted/diseased heart in terms of changes in the biochemical and the electrophysiological properties which are related to the dysfunction of ion channels.

SOME PROPERTIES OF THE VULNERABLE SUBSTANCE IN THE INFARCTED HEART

The unknown etiology of the VS becomes an obstacle in developing a novel AAD for eliminating ventricular arrhythmias in a diseased heart. Some of its properties have unravelled to some extent the mystery of an infarcted heart.

Depletion of norepinephrine in an infarcted heart Following an onset of acute myocardial infarction norepinephrine (NE) is rapidly released from the myocardium, leading to a depletion status in an infarcted heart[11]. The enhanced release of NE is correlated with the presence of ischemic arrhythmias. Abrupt withdrawal of propranolol after chronic medication frequently induces cardiac arrhythmia and an increase in severity of cardiac arrhythmias is also linked with an increase in NE release[12,13]. A heart with overt congestive cardiac failure is at risk to develop cardiac arrhythmias and is also presented with a depletion of NE.

The spontaneous VF and programmed electric stimulation (PES)-induced ventricular tachycardia (VT) are not frequently induced in a normal heart. However, these occur in a chronic infarcted heart due to the existence of a vulnerable substrate (VS)[2]. A progressive and sustained depletion of NE in the non-infarcted region of a heart possibly exerts an important role in the formation of VS.

A rapid depletion of NE is noted in an infarcted zone (IZ) during the acute phase of myocardial infarction. The NE concentration in the non-infarcted zone (NIZ) remains intact after coronary occlusion because of no development of ischemia over there. A depleted NE in the NIZ can not be found until 24 h after AMI. It is progressive and sustained, and eventually depletion of NE in the NIZ approaches to the level of the IZ[14]. It resembles the depletion of acetylcholine developed at the endplate after denervation of skeletal muscle causing an abnormal response to the transmitter. Under persisted depletion of NE in an infarcted heart, and in a congestive cardiac failure, the response to NE and the impulses of the sympathetic nerve could be altered. It is evidenced that the cardiac arrhythmias induced in an infarcted heart are greatly exaggerated in response to an isopreterenol challenge[13].

Norepinephrine modulating ion channels via the activation of α- and β-adrenoceptors Abnormal release of NE in the myocardium may trigger cardiac arrhythmias due to activation of α- and β-receptors as fol-

lows：

Activation of β-receptors. Some ion channels such as I_K, I_{Ca}, I_f (the inward I_{Na} current in the phase 4 of the action potential responsible for the local depolarization), and I_{Cl} are required for a process of phosphorization of the ion channels to increase the conductance of ion flux. The achievement of phosphorization is dependent upon the presence of cAMP and takes place at the nucleotide binding domain between the S6 of the transmembrane peptide chain and the -COOH end inside the cytosol[15]. The β-receptor activation promotes opening of the channels to increase these currents and eventually shortens the APD. The APD is determined mainly by the balance between the inward currents I_{Ca} and I_{Na}, and the outward current $I_K + I_{to}$, simplified as：APD (I_{Na} and I_{Ca})/($I_K + I_{to}$). A shortened APD is a cause of inducing reentry mechanism, and the activation of I_{Na} and I_{Ca} also possibly leads to the triggered activity[16] for development of the early after depolarization (EAD)[17], which is recognized as a single cell model of the *torsade de pointes*. Both the shortening of APD and the formation of EAD are closely related to the appearance of cardiac arrhythmias. In general, the trigger mechanism takes part in a given tachycardia when the reentry of impulse is the main mechanism involved.

The opening of the I_K channel by the released norepinephrine via the activation of the β-receptor is likely to provoke arrhythmogenesis. An alleviation of arrhythmias can be achieved by a reduction in NE release, and furthermore, the APD prolonging effect of the pure Class Ⅲ agent E4031 is lost in the presence of activated β-receptor by an isopreterenol challange. Isopreterenol was able to eliminate the prolongation of APD by *d*-sotalol via β-receptor activation mechanism and *d*,*l*-sotalol retained the ability to lengthen the APD totally, ignoring the isopreterenol challenge[18]. Epinephrine iv could cause dispersion of QTc (the corrected QT interval) in patients suspected with long QT syndrome (LQTS)[19] who are at high risk to ventricular arrhythmias under stress.

Activation of α-receptors. An increment in free Ca^{2+} in the cytosol is possibly involved in the development of cardiac arrhythmias and is the consequence to both an opening of the receptor operated channel via the α_{1A} receptor and an enhanced intracellular release of Ca^{2+} by activated α_{1B} receptor mediated by IP_3. Furthermore, the temporary outward potassium ccurrent I_{to}[20] and the inward rectifier potassium current I_{K1}[21], which affect the APD, are opened under the influence of the activated α-receptors. The activation of both the α- and β-receptors was found to be linked with an exacerbated cardiac arrhythmia[22].

The imbalance of conductance in ion channels results from the abnormal distribution of cations in myocardium, diminished K^+, and elevated Na^+ and Ca^{2+} in the cytosol[23]. It forms the ionic basis for development of cardiac arrhythmias attributed at least partly to the release of NE.

Reduction in SOD activity involved in vulnerable substrate in the non-infarcted zone A reduction in the SOD activity in NIZ is not significantly observed in the acute phase until a couple of days after AMI. The process is progressive and long lasting, reaching a very low level in the IZ in a chronic infarcted rat heart[24]. In contrast, the MDA production in NIZ does not vary significantly. The ATP levels in the NIZ decrease only temporarily and return to the normal levels 24 h after AMI[14]. The energy supply remains normal and no excess peroxide product exists in the NIZ in a chronically infarcted heart. The infarcted heart, however, is at risk to be attacked by oxidative stress due to a reduction in SOD activity. This may be one of the vulnerable properties of the NIZ. Drug interventions have been partially effective in increasing NE and SOD activity to improve the VS property[24]. The VS can be considered as a non-specific lesion in myocardium caused by infarction, hypertrophy, and ischemia.

Is hypertrophy the morphological basis for the VS Morphological changes in the NIZ were evident and presented by hypertrophy in the wall of the left ventricle and septum 4 days after infarction in rat heart[25]. Hypertrophied heart may be considered as a sort of ischemia, as an increase in the distance for oxygen diffusion between capillary to the center of a myocyte, results in an uneven repolarization. An increase in the length of impulse conduction may play a role to cause diversity in repolarization of a hypertrophied heart. The APD, in hypertrophied ventricle, developed by either partial ligation of the abdominal aorta or chronic medication of levothyroxin, and the MAPD (mono-phasic APD) 24 h after AMI were reportedly prolonged indicating that repolarization had been altered in diseased hearts. It is thus reflected that the ion channels responsible for the repolarization process are altered in hypertrophied hearts. An increase in the dispersion of QT in SHR, where a potential of ventricular hypertrophy exists, is associated with a risk of arrhythmogenesis[26]. The expression of mRNA

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of K^+ current family in a failing heart was altered, mainly in a reduced manner[23]. Ventricular hypertrophy is, thus, an independent risk to develop cardiac arrhythmia, in which the altered transmembrane signaling, accumulated collagen, and fibrosis in myocardium contribute to inhomogeneous electrophysiology. The vulnerable property of arrhythmogenesis of an infarcted heart is partly, at least, mediated by hypertrophy of the ventricle.

DISORDER OF ION CHANNELS AND CARDIAC ARRHYTHMIAS

Recently the awareness of molecular mechanisms involved in congenital LQTS greatly promoted the understanding of mechanisms of affected ion channels underlying the malignant ventricular arrhythmias.

Awareness of individual mutation causing ion channel dysfunction in LQTS A great deal of information has been developed in molecular biology to understand the insights of the mode underlying the congenital LQTS[15,27]. There are some mutations in individual ion channel related genes discovered as an etiological factor to present a long QT interval in ECG in individual member of the affected family. Sudden cardiac death by malignant cardiac arrhythmias is induced by two kinds of mutations which develop abnormal potassium and sodium ion channels in the myocardium. The I_{KS} (the slow component of I_K) ion current is altered by mutations in either the KvLQT1 gene, causing a disordered α-sub-unit (the LQT1), or hMINK gene, causing dysfunction of the β-sub-unit[28]. The abnormal I_{Kr} (the rapid component of I_K) caused by mutations of HERG gene in LQT2[29] is currently the target for extensive investigation. The cardiac sodium channel could be rendered abnormal as the consequence of mutation of SCN5A in LQT3[30] and R1623Q[31].

We have also discovered an early appearance of a stopping codon found in a member from a LQT family. It causes a loss of function via a very short channel and presents an inherited LQTS in the ECG[32]. Other mutations, one in a normal QT persons HERG gene, caused by an insertion of three additional amino acids and the other by cysteine replacing serine in HMINK gene were also found. However, these resulted in no change in QT interval. Probably, the two mutations are not crucial enough to alter the ion channel function[32].

Disordered multiple ion channels in hypertrophied ventricle The function of ion channels is changed by the development of hypertrophy in a diseased heart. A reduction in I_{to} and I_{K1} is one of the main manifestation of a failing enlarged heart[33]. In a hypertrophied model produced by chronic levothyroxin, cardiac arrhythmias caused by ischemia/reperfusion were markedly exaggerated with high incidence of ventricular fibrillation[34]. Thus this model of ventricular hypertrophy was adopted to investigate the changes in ion channels to unravel the possible correlation between disordered ion channels and severe cardiac arrhythmias. The APD was lengthened accompanied with ventricular hypertrophy and no significant changes in V_{max} of the action potential were observed. By using the whole cell holding technique the I_{Ca} of this type of hypertrophied myocardium was enhanced[35]. This can explain the prolonged APD. An alteration in conductance however is not limited to a single ion channel, thus, along with the changes in I_{Ca}, the I_K and I_{Na} were also altered[36]. The I_{Na} channels were also affected non-specifically showing a diminished state. There was a decrease in I_{Na}, an increase (including a transient decrease) in I_K, and an increase in I_{Ca}[37], as summarized in Tab 1. The pattern of the diseased ion channels in a hypertrophied ventricle is totally different from the inherited LQTS. It is also likely to be different in some aspects of disordered ion channels in different heart diseases, but the basic fact is likely to be the same that a disorder of ion channels is presented in a diseased heart is multiple in nature. A reduction in I_{Na} is interesting, indicating that an abnormal process is not only in-

Tab 1. Comparison of altered ion channels in LQTS and acquired hypertrophied myocardium.

Diseases	Affected site	Ion channels	Dysfunction
LQTS			
LQT_1	KvLQT1 gene	I_{KS} α subunit	Reduced
	hMINK gene	I_{KS} β subunit	Reduced
LQT_2	HERG gene	I_{Kr}	Reduced
LQT_3	SCN5A gene	I_{Na}	Inactivation Delayed
Hypertrophied myocardium	Lipid membrane	I_{Na}	Reduced
		I_{to}	Reduced
		I_{Kr}	Reduced
		I_{KS}	Enhanced Reduced
		I_{Ca}	Enhanced

volved in repolarization, but also in depolarization of an affected myocardium. An increment in I_{Ca} in a hypertrophied heart is agreement with the increased Ca^{2+}, Mg^{2+} ATPase activity in the sarcolemmal[38] and mitochondrial[39] membrane in the hypertrophied rat heart produced by chronic levothyroxin.

THERAPEUTIC INTERVENTIONS FOR THE ION CHANNELS DISORDER

In congenital LQTS where mutations in the related gene specially cause an altered individual ion channel, propranolol effectively shortens the QTc interval in the congenital LQT_2 (Mutations in the HERG gene). Lidocaine and mexiletine are the drugs of choice to reduce QTc in congenital LQT_3, suitable enough to prevent sudden cardiac death[40].

In a diseased heart abnormal functioning of channels is secondary to a primary lesion in myocyte, such as a damaged lipid membrane where ion channels assemble. Thus ion channel disorder caused by VS is non-specific and multiple *vs* the single channel affected in inherited LQTS. An AAD affecting multiple ion channels seems promising to restore the diseased state of the multichannel. As a matter of fact amiodarone which exerts a blockade on several ion channels is beneficial for the ventricular arrhythmias in an infarcted heart. The superiority of sotalol in controlling ventricular life-threatening arrhythmias as compared with *d*-sotalol, which possesses a pure I_{Kr} blocking action, is based on its β-blocking activity. The influence of β-blockers on the life-threatening arrhythmias is based on several factors. The non-specific blockade of multiple channels can be beneficial against the over-activity of sympathetic nerve system which always precedes tachyarrhythmias[41]. The multiple ion channel disorder is the result of pathological changes in the lipid membrane and myocardium, so a relief in the ischemic lesion by pharmacological interventions up-stream to the ion channel disorder, can offer an alternative route to diminish the ion channel dysfunction. Without direct interaction with ion channel pharmacological interventions are likely to help in suppressing arrhythmias with less toxic effects seen on the ion channels[42].

A novel antiarrhythmic agent CPU-86017 possessing a blocking action on multiple ion channels is effective in supressing arrhythmia in various animal models[43,44]. It exerts a blockade on the I_{Na}, I_{Ca} and I_K[43,45]. It exerts a bi-phasic impact on the APD, prolonging and shortening at low and high concentrations, respectively. This phenomena is similar to that exhibited by azimilide[46] which causses a blockade on the I_{Kr} and I_{Ca}, creating a biphasic change in APD. A prolongation of APD caused by blocking of I_{Kr} is opposed by blocking of I_{Ca} which shortens APD at higher concentrations. This property improves its electrophysiological property of use-dependence to suppress arrhythmias. This biphasic influence on the APD is suitable for preventing both the appearance of very long APD, which is predisposed to *torsades de pointes*, and a short APD where the reentry of impulse may emerge.

It is potentially toxic for an antiarrhythmic agent to interact with an individual ion channel[42]. Therefore, an AAD affecting multiple ion channels[7,8,37] in a diseased heart, or a drug acting up-stream of the diseased ion channels[47], may be favorable for cardiac arrhythmias, and may hopefully reduce the incidence of proarrhythmias.

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病变心脏中的易损基质及多离子通道损害为抗心律失常药的新靶点

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关键词 抗心律失常药；心肌梗死；肥大；去甲肾上腺素；左甲状腺素；离子通道；CPU 86017

心血管疾病主要死因是致命性心律失常，对它的治疗仍是一个问题. 当前Ⅰ类及Ⅲ类药均不推荐用于控制室性心律失常，由于药效差及增加死亡率，对病变心脏有毒性. 梗死心脏中非梗死区(NIZ)中形成易损基质(VS)，如去甲肾上腺素耗竭，SOD 活性降低，心肌肥大，APD 延长及 QT 离散度增加等. 慢性给左甲状腺素可形成心肌肥大及加重缺血/再灌注性心律失常，此模型有 VS 的特点. 离子通道的病变类型在先天性 LQTS 与后天性心脏病中有明显的不同. 先天性 LQTS 是单一离子通道的改变. 我们发现在 HERG 中一个新突变-提前终止密码，使 QT 延长. 而后天性心脏病的心肌肥大是多离子通道病变而非特殊性. 后天性心脏病中离子通道病变是继发于 VS 病变对脂质膜的影响. VS 及多离子通道的病变可作为药物治疗病变心脏心律失常的新靶点.

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