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Role of Sodium and Calcium Dysregulation in Tachyarrhythmias in Sudden Cardiac Death

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Abstract

Despite improvements in the therapy of underlying heart disease sudden cardiac death (SCD) is a major cause of death worldwide. Disturbed Na and Ca handling is known to be a major predisposing factor for life-threatening tachyarrhythmias. In cardiomyocytes many ion channels and transporters, including voltage-gated Na and Ca channels, cardiac ryanodine receptors, Na/Ca-exchanger and SR Ca-ATPase are involved in this regulation. We have learned a lot about the pathophysiological relevance of disturbed ion channel function from monogenetic disorders. Changes in the gating of a single ion channel and/or the activity of an ion pump suffice to dramatically increase the propensity for arrhythmias even in structurally normal hearts. Nevertheless, patients with heart failure (HF) with acquired dysfunction in many ion channels and transporters exhibit profound dysregulation of Na and Ca handling and Ca/calmodulin dependent protein kinase, and are especially prone to arrhythmias. A deeper understanding of the underlying arrhythmic principles is mandatory if we are to improve their outcome. This review addresses basic tachy-arrhythmic mechanisms, the underlying ionic mechanisms and the consequences for ion homeostasis, and the situation in complex diseases like HF.

Keywords

sodium; calcium; calcium/calmodulin-dependent kinase II; alternans; arrhythmias

Introduction

Sudden cardiac death (SCD) refers to a sudden unexpected death from cardiac causes, and is a major cause of death worldwide.[1] In patients with structural heart disease arrhythmias are the main cause of death.[2] Despite improvements in primary and secondary prevention with substantial decline in mortality of coronary heart disease in recent years,[1,3] SCD rates have declined to a much lesser extent.[4] Implantable cardioverter-defibrillators (ICDs) can reduce cardiovascular mortality in high risk patients, but prevention of SCD is particularly

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challenging because the majority of cases occur in individuals without a prior diagnosis of cardiac disease or other clear risk factors for SCD. Thus, understanding the mechanisms of SCD is crucial for both identification of patients at risk and also for developing novel medical or interventional treatment.

SCD is descriptive of a clinical event, but is not a well-defined disease with one specific underlying mechanistic pathophysiology. In contrast to contractile failure, SCD is a consequence of the immediate and complete inability of the heart to maintain the circulation. The most likely SCD causes are lethal cardiac arrhythmias like ventricular tachycardia (VT) or ventricular fibrillation (VF), although bradyarrhythmias also play an important role.[5] The imprecise definition may also include pulseless electrical activity e.g. as a consequence of large pulmonary embolism.

The underlying mechanisms of life-threatening ventricular tachyarrhythmias are manifold. They can occur as a consequence of isolated channelopathies in a structurally normal heart. However, more frequently, they are secondary to substantial dysregulation of intracellular Ca and Na handling that accompanies contractile dysfunction in HF. There is also a growing body of evidence that Ca/calmodulin-dependent kinase II (CaMKII) is involved. CaMKII regulates many Na and Ca handling proteins (and is also regulated by Ca) thereby influencing both contractile function and arrhythmogenesis. This review will discuss the mechanisms linking Ca and Na handling to arrhythmogenesis with special focus on CaMKII.

Excitation-contraction coupling

To understand arrhythmogenesis, basic knowledge about the fundamental principles of excitation-contraction coupling is required (Figure 1). Cardiac excitation is based on sarcolemmal ion fluxes that are tightly coupled to cytosolic Ca and contraction.[6] Excitation is initiated by opening of voltage-gated Na channels and Na current influx (I_{Na}) leading to the rapid action potential (AP) upstroke (phase 0).[6,7] Phase 0 is limited by fast I_{Na} inactivation and the activation of transient outward K channels ($K_V4.2$, $K_V4.3$, and $K_V1.4$). These K channels generate transient outward K current (I_{to}) resulting in an early and partial repolarization i.e. the AP notch (phase 1), which is followed by a plateau phase (phase 2). During the latter, membrane conductance falls dramatically as inward and transient outward currents inactivate. Due to the time- and voltage-dependent gating properties of delayed and inward rectifier K channels K current fluxes are small and only capable of balancing the relatively small remaining inward Ca current (I_{Ca}) via L-type Ca channels (LTCC, $Ca_v1.2$). This is why the repolarization rate at plateau voltages is slow. Moreover, because of high membrane resistance, even small currents such as Na/Ca exchange current (I_{NCX}), Na/K-ATPase current (I_{NaK}) or I_{Ca} reactivation can destabilize the plateau membrane potential resulting in arrhythmias. I_{Ca} (which activates more slowly than I_{Na}) also progressively decays during the plateau. In ventricular cells, phase 3 repolarization ensues as K currents slowly activate (I_{Ks}, carried by Kv7.1, *KCNQ1*) or undergo voltage-dependent recovery from inactivation (I_{Kr}, carried by hERG, *KCNH2*), and I_{K1} (carried by Kir2.x channels) progressively contributes as the membrane repolarizes. I_{K1} also stabilizes diastolic V_m near −80 mV during phase 4. In pacemaker cells, the relative paucity of stabilizing I_{K1}[8] together

with the prominence of the hyperpolarization-activated non-specific cation current I_f (HCN channels) and Ca release driven I_{NCX}, are mainly responsible for diastolic depolarization leading to AP initiation and pacemaker function.[6]

The cardiomyocyte membrane (sarcolemma) has transverse invaginations called T-tubules (~200 nm diameter) that reach deep into the myocytes interior. T-tubules make close contact with enlarged junctional sarcoplasmic reticulum (SR) cisternae, with only a 14 nm wide dyadic cleft that separates the SR and T-tubular membranes. LTCCs are highly concentrated in the T- tubules at these junctional clefts and are in close proximity to cardiac ryanodine receptors (RyR2), the SR Ca release channel (Ca release microdomain). This LTCC-RyR2 proximity at the dyadic cleft means that Ca ions that enter via I_{Ca} cause local cleft [Ca] to be very high, sufficient to trigger the opening of RyR2 clusters responsible for SR Ca release during excitation-contraction coupling. This Ca-induced Ca release amplifies the sarcolemmal Ca influx and depending on species and heart rate the SR Ca release accounts for 70 to 92% of total Ca increase during systole. Total Ca is heavily buffered (~100:1), but free cytosolic [Ca] typically increases from 100 to 600 nmol/L, which leads to myofilament activation and contraction (systole). The $[Ca]_i$ rise is transient since I_{Ca} inactivation and RyR2 closure limit cytosolic Ca entry, and at the same time Ca removal pathways are activated. For Ca removal, the two major pathways are: SR Ca-ATPase (SERCA2a) and sarcolemmal Na/Ca exchange (NCX1), although a tiny fraction of Ca can be extruded by the sarcolemmal Ca-ATPase (PMCA) and mitochondrial Ca uniporter (MCU). During steady-state, the proportion of Ca transported into SR and out of the cell correspond exactly to the amount of Ca released from the SR and sarcolemmal Ca influx, respectively.

CaMKII

CaMKII is a serine/threonine kinase that can be activated by Ca/calmodulin binding to its regulatory domain. This activation results in the phosphorylation of target proteins including RyR2, $Na_V1.5$, LTCC and phospholamban (the negative regulator of SERCA2a).[9,10] Therefore, CaMKII is crucially involved in the regulation of excitation-contraction coupling.

CaMKII assembles into a dodecameric holoenzyme consisting of two stacked hexamers. One of the target proteins of CaMKII is the regulatory subunit of an adjacent CaMKII monomer. This auto-phosphorylation results in augmented activation that persists even after dissociation from Ca/CaM and provides an integrated response from the short-term fluctuations in intracellular Ca. It was also shown that reactive oxygen species (ROS)-dependent oxidation of CaMKII at two methionine residues at the regulatory domain (M281/282) results in autonomous activation similar to autophosphorylation.[11] Thus, CaMKII can link increased ROS to their downstream effectors. Increased expression and activity of CaMKII[12,13] has been linked to contractile dysfunction and arrhythmias in HF and upon conditions of increased ROS production.[14–20]

Mechanisms of electrical instability

Ventricular tachycardia or fibrillation are the result of cell membrane hyperexcitability, disturbed repolarization or defective conduction of the electrical wavefront across the myocardium.[21] The presence of an electrically inactive scar tissue that often develops after

myocardial infarction forces the wavefront to propagate around this line of block. The wavefront then enters the area behind the scar. If that wavefront reaches the back of the obstacle from multiple directions simultaneously (or near the same time) then the waves will annihilate (Figure 2A). However, if unidirectional block (often coupled with decremental conduction) exists around one side, the wavefront can reenter and re-excite tissue in front of the unidirectional block (Figure 2A). This can lead to stable macroscopic re-entry. Reentry can also occur around other functional obstacles (e.g. depolarized tissue), and can take the form of a rotor.[21,22] Stable rotors lead to monomorphic VT. If the waves that propagate outward from a rotor develop wavebreaks, additional rotors are generated, which may lead to polymorphic VT and VF.[22] This development is much more likely under conditions of altered excitation, repolarization or conduction due to disturbed ion channel function (Figure 3). A typical cause for this electric remodeling is structural remodeling associated with cardiac disease secondary to advanced age, increased oxidant stress, hypertension, diabetes, tissue injury or inflammation.[21] However, the disturbed function of ion channels that underlies these changes in excitation, repolarization or conduction can also occur in structurally normal myocardium. Abnormal impulse conduction with consequent reentrant excitation can also be a consequence of Ca alternans (Figure 3). This is an example of how Ca dysregulation can cause reentry, which is the most common mechanism of electrical instability.

Beside reentry, triggered activity is another important mechanism of electrical instability. The latter is the result of an imbalance of ion currents within a single cardiomyocyte. Such imbalances can be classified as either early or delayed depending on their occurrence during the action potential. Early afterdepolarizations (EADs) occur during the plateau phase of a cardiac action potential, while delayed afterdepolarizations (DADs) disturb the diastolic membrane potential after AP repolarization is complete (Figure 2B). Both EADs and DADs can reach the threshold inducing premature ventricular contractions, which can degenerate into monomorphic or polymorphic VTs.

Early afterdepolarization

EADs occur during the AP and are a consequence of increased inward currents or reduced repolarization reserve (reduced outward K currents).[6] The plateau phase of the AP is especially vulnerable since repolarizing and depolarizing currents are small and nearly balanced. During this phase, small alterations in the amplitude of even one ionic current can result in the generation of an EADs. We have learned much about the fundamental mechanisms of triggered activity by studying familial disorders with prolonged repolarization. For example, congenital long QT syndrome 3 is characterized by profound AP prolongation due to increased persistent or late Na current (late I_{Na}),[15,23] EADs are a major trigger for tachyarrythmias, but can also occur at low heart rates (where AP duration is intrinsically long). The long AP duration allows for reactivation of I_{Ca} at plateau potentials. The resulting inward current creates an EAD as a depolarization in the otherwise monotonically decaying plateau voltage.[24,25] Amongst the long QT syndromes, the Timothy syndrome is a very rare form, caused by a mutation in $Ca_V1.2$ that prevents normal I_{Ca} inactivation. This disease is characterized by AP prolongation, increased QT intervals, life-threatening arrhythmias, and multisystem defects. Similar to other causes of AP

prolongation, I_{Ca} reactivation is a major cause of EAD formation. Interestingly, pathological AP prolongation is a prominent feature of a proarrhythmic electrical remodeling in HF,[26,27] but can also occur in response to drugs that inhibit K channels (especially I_{Kr}). This highlights the importance of this fundamental arrhythmic mechanism.

Beside these well-studied EADs arising during long AP plateaus via I_{Ca} reactivation, there is now compelling evidence that some EADs are initiated by SR Ca re-release during the AP that causes inward I_{NCX}. These EADs are more common during repolarization, and are sometimes called phase 3 EADs. The inward I_{NCX} may only cause a weak depolarization, but that can be amplified by re-activation of $I_{Ca,}$[2829] depending upon the voltage. That is, in atrial (and rodent ventricular) APs with I_{NCX}-prolonged late and plateau at voltages below −40 mV (where I_{Ca} reactivation does not occur), EADs may be driven by non-equilibrium reactivation of I_{Na}, which is facilitated by increased SR Ca release.[30]

Delayed afterdepolarization

DADs are a consequence of cytosolic and SR Ca overload.[31] Both increased cytosolic and SR luminal Ca increase the diastolic open probability of cardiac RyR2.[6] Ca sparks are elementary SR Ca release events that occur if a cluster of RyR2 open. During systolic Ca-induced Ca release, Ca sparks are synchronized within the cell and summate to form the Ca transient. Spontaneous Ca sparks are mainly responsible for diastolic SR Ca release and diastolic SR Ca leak via RyR2.[32,33] Since RyR2 is in relatively close proximity to the NCX, this localized $[Ca]_i$ elevation drives inward I_{NCX}. Note that the stoichiometry of Na/Ca exchange ($3Na^+$:$1Ca^{2+}$) meaning that Ca extrusion is accompanied by a net inward movement of one positive charge via I_{NCX} which is almost entirely responsible for what used to be called transient inward current I_{ti}.[31] If this I_{NCX} is large enough, it can cause and appreciable DAD which can trigger an arrhythmic AP. Individual Ca sparks normally do not produce enough I_{NCX} to produce a measurable DAD because they are isolated unsynchronized events. However, at higher SR Ca content the Ca sparks are larger in amplitude and nearby RyR2 clusters are more sensitive to activation resulting in a cell-wide Ca wave with sufficient I_{NCX} to cause DADs and triggered APs. Sympathetic stimulation can drive up SR Ca content and increase the propensity for Ca waves and triggered beats.

In the intact heart the I_{NCX} produced by a Ca wave in a single myocyte is insufficient to trigger an appreciable DAD or AP because all of the neighboring cells can effectively clamp that single cell at the diastolic voltage. However, when these Ca waves and consequent I_{NCX} are synchronized regionally among many cells (by the prior AP and similar RyR2 recovery kinetics), that region can initiate triggered beats as premature ventricular contractions for the whole heart.[34,35] The heart is relatively protected from these triggered arrhythmias initiated via EADs and DADs, but under pathological conditions due to either genetic ion channel/transporter mutations or acquired diseases like HF both the cellular propensity for EADs and DADs and their ability to cause whole heart premature ventricular contractions can be greatly increased.[34–37]

Cardiac alternans

Cardiac alternans is a known risk factor for cardiac arrhythmias and SCD.[38–40] The transition from monomorphic VT to polymorphic VT or VF requires breaks in the wave propagating from a stable rotor. During VT, cardiomyocyte Ca cycles at high rates. The time for intracellular Ca removal is drastically shortened and can elevate diastolic $[Ca]_i$ and limit SR Ca load.[41] This can also encroach upon the recovery time of the I_{Ca}-induced SR Ca release.[42,43,64,65] Normally, $[Ca]_i$ is tightly controlled, but Ca dysregulation can predispose to afterdepolarizations and cardiac alternans.[44–47] Cardiac alternans are alternating beats with large/small amplitude Ca transient and long/short APD (Figure 4A). Most common in large mammals are electromechanically (or V_m-Ca) concordant alternans in which the large Ca transient and contraction is associated with the longer APD. However, V_m-Ca discordant alternans can also occur. Alternans can also be spatially concordant, where all regions of the ventricle are in phase with each other, or spatially discordant where different regions are out of phase with each other. As we will see the Ca and V_m changes are usually functionally linked, but both can occur independently.[44]

Repolarization alternans

Alternation in APD is called repolarization alternans. Since this type of alternans involves membrane potential, it can be clinically observed as T-wave alternans (TWA).[48] TWA has been shown to be associated with cardiac arrhythmias and SCD.[49–51] TWA is not restricted to a specific underlying disease but can be observed in HF, Brugada syndrome, and long QT syndrome.[52]

TWA can result from changes in sarcolemmal ion current recovery (typically of I_{Na} or I_{Ca}) manifested by a steep slope of cellular APD restitution.[53] This type of TWA typically occurs at high heart rates with reduced diastolic intervals.[48,54,55] The dependence of APD and conduction velocity (CV) on the preceding diastolic interval are called APD restitution and CV restitution, respectively. Shorter diastolic intervals result in shorter APD and slower CV.[45] Both APD and CV restitution critically depend on the speed of recovery from inactivation of sarcolemmal ion channels. Nevertheless, other mechanisms, for instance SR Ca release, can also contribute to APD restitution changes. Intracellular Ca released from the SR inactivates I_{Ca}. A large SR Ca release could, therefore, result in a more pronounced Ca-dependent inactivation of I_{Ca}, which would influence APD restitution.

CV restitution, on the other hand, mainly depends on Na channel recovery.[56] This is due to the fact that conduction velocity depends on AP upstroke velocity, and the latter is determined by the magnitude of I_{Na}. Na channel recovery is usually very fast, thus, CV restitution occurs only at very high heart rates, as would be the influence of Na channel recovery on APD restitution. However, under conditions of slowed Na channel recovery, the impact on CV restitution (and also APD restitution) may already occur at much lower heart rates. This is important, since slowed Na channel recovery has been shown to be a feature of many cardiac diseases like HF,[14,57] or ischemia[56,58,59] (where CaMKII may be involved)[14] and Brugada syndrome.[60]

As mentioned above, APD restitution depends on sarcolemmal ion channel recovery. Amongst them, L-type Ca channels are very important. I_{Ca} is the major inward current during the AP plateau.[6] As stated above AP plateau is the most vulnerable phase of the AP. This explains, why inhibition of I_{Ca} has been shown to reduce the slope of the APD restitution curve. In addition, the recovery of Ca channels is slower compared to, for instance, Na channels. Therefore, Ca channels influence APD restitution already at lower heart rates. Interestingly, since I_{Ca} also determines SR Ca load, and vice versa, APD alternans and Ca alternans are functionally linked.

Repolarization alternans can be either spatially concordant or discordant.[48,61] It was shown that Na channel recovery is critically involved in spatially discordant alternans.[61,62] Since spatially discordant alternans is accompanied by changes in conduction velocity, both T wave and QRS are affected resulting in T-wave and QRS alternans (Figure 6). Repolarization alternans can be proarrhythmic by two mechanisms. First, spatially discordant alternans results in spatial dispersion of repolarization providing a substrate for reentry.[48] Second, at high heart rates alternans can promote conduction block, which may trigger rotor formation. Alternans-dependent arrhythmias are, therefore, most likely generated under conditions of increased heart rate like during exercise or occur secondary to a stable rotor-dependent ventricular tachycardia. In fact, alternans may mechanistically explain why a stable ventricular tachycardia may degenerate into a multiple wavelet-driven polymorphic ventricular tachycardia or VF.[63,64]

Importantly, if APD is substantially prolonged, which is a typical feature of HF [26,27] or long QT syndrome, [65] ion channel recovery is already impaired at lower heart rates. Even without AP prolongation, if Na channel recovery is impaired like in HF[14,57], ischemia[56,58,59] and Brugada syndrome[60] alternans-dependent arrhythmias can occur at much lower heart rates.

Ca alternans

From the surface electrical measurements of an electrocardiogram it is impossible to state if APD alternans is accompanied by Ca alternans, or whether one leads to the other. However, extensive work over the past years has shown that Ca and APD alternans usually co-exist, are mechanistically linked and that Ca-driven alternans appear to be more clinically relevant in the setting of heart disease.[53]

Alternans start to occur as pacing rate is increased, and Ca alternans occur even when myocytes are voltage clamped with identical V_m waveforms, consistent with Ca-driven alternans.[44,45,66]

In the absence of voltage clamp those Ca alternans also cause APD alternans, and there are logical reasons why a larger vs. smaller Ca transient would alter APD. The two most prominent $[Ca]_i$-dependent currents are I_{Ca} and I_{NCX}. A large Ca transient would a) strengthen Ca-dependent inactivation of I_{Ca} which would shorten APD, and b) drive increased inward I_{NCX}, which would prolong APD. In mammals with prominent AP plateaus, concordant V_m-Ca alternans usually predominate, suggesting that the I_{NCX} effects are more powerful contributors to alternans. However, some conditions could shift this balance to favor a predominant role for I_{Ca} inactivation and discordant V_m-Ca alternans. As

stimulation rate increases alternans start at a certain threshold and the alternans ratio (large:small Ca transient amplitude or APD) increases progressively. This can be seen as alternans in the amount of SR Ca release in direct measurements of intra-SR free [Ca] ($[Ca]_{SR}$), in both isolated myocytes and whole heart (Figure 4A).[42,43]

Several factors contribute to alternans, and they seem to follow a sequence. The first step seems to be an encroachment on RyR2 recovery so that SR Ca release decreases, despite unaltered APD, I_{Ca} and $[Ca]_{SR}$.[42,43,67]

This is because RyR2 restitution is much slower than normal I_{Ca} restitution. The partial failure of SR Ca release at this first small beat allows improved RyR2 recovery at the next large beat, but then the cycle repeats. SR Ca release alternans can appear at heart rates where the consequent APD alternans are not yet detectable (Figure 4B). As Ca release alternans grow they are amplified by alternating changes in SR Ca load, i.e. SR Ca load alternans (Figure 4C). The small release limits Ca-dependent inactivation of I_{Ca}, thereby increasing Ca influx and load for the next (large) beat. The small Ca transient also drives less Ca extrusion via NCX, which limits Ca loss at the small beat. Then at the large beat there is greater Ca-dependent I_{Ca} inactivation and greater Ca efflux via NCX, which reduces cell and SR Ca load, setting the scene for very stable alternans, up to 6–7 Hz (150 ms cycle length) in rabbit hearts (Figure 4C). The steep non-linear dependence of SR Ca release on diastolic SR Ca load[41,68] enhances the impact of the SR load alternans on Ca release alternans.[46] At even higher stimulation rates, shorter diastolic intervals or more depolarized diastolic voltage, one can encroach on I_{Ca} (or even I_{Na}) restitution, which may also exacerbate a sort of Ca-driven alternans (smaller I_{Ca} causes smaller Ca transient and APD). But here the lines become blurred with the electrical, restitution-driven alternans involving APD and CV restitution, as discussed above.

A number of factors can influence the pacing rate at which alternans is observed. Inhibition of glycolysis, mitochondrial energetic limitations, decreased SERCA function and redox modification of RyR2 can all favor alternans.[69–72] All of these factors may be relevant in pathophysiological conditions like HF, thus enhancing the propensity for alternans and arrhythmogenic sequelae in these conditions.

Similar to repolarization alternans, Ca alternans can be spatially in phase (concordant) or out of phase, i.e. discordant, in different regions of a single myocytes[73–75] or hearts, and spatially discordant alternans have been associated with lethal VTs and VF in patients.[48,76]

Arrhythmias in HF and ischemia/reperfusion

Despite improvements in HF therapy and ischemia/reperfusion associated myo-cardial damage, it has proven difficult to develop antiarrhythmic treatments and prevent SCD. Conventional ion channel blockers that are used as antiarrhythmic drugs are known to induce arrhythmias in structural heart disease.

There is an increasing body of evidence that HF and ischemic heart disease are accompanied by alterations in intracellular Na and Ca handling. Both conditions are characterized by an increased generation of ROS,[77–79] which may contribute to disturbed Na and Ca handling.[80]

Changes in intracellular Na and Ca handling are associated with electrical instability and many of these alterations are linked to both contractile dysfunction and arrhythmias.

Late Na current

As stated above, APD is increased in HF.[27] Beside reduction of K current expression, increased magnitude of late I_{Na} has been shown to contribute to AP prolongation in HF,[81] and after myocardial infaction.[82] Late I_{Na} is generated by dysfunctional inactivation of cardiac voltage-gated Na channels $Na_V1.5$.[83] The detailed molecular mechanism is not fully understood.[84]

Although late I_{Na} has a small amplitude compared with peak I_{Na} it persists for hundreds of milliseconds during the cardiac AP,[85] providing a source for increasing $[Na]_i$.[14,15] Increased $[Na]_i$ is a well-known feature of HF, ischemia/reperfusion or other conditions of increased ROS production and can contribute to contractile dysfunction and arrhythmias.[15,18,23,86–90]

The late I_{Na}-dependent prolongation of the AP plateau renders the membrane potential vulnerable for EADs (Figure 5).[15] A similar arrhythmic mechanism can be found in familial long QT syndrome 3 (LQT3). Mutations in the gene encoding for $Na_V1.5$ (*SCN5A*) have been shown to increase late I_{Na} leading to AP prolongation and EADs.[91,92] Transmural differences in late I_{Na} might also increase dispersion of repolarization,[93] which underlies the development of torsade de pointes tachyarrhy-thmias. In addition, late I_{Na} is involved in cardiac alternans: ischemia-induced spatially discordant repolarization alternans has been shown to be prevented by inhibition of late I_{Na}.[94]

Beside AP prolongation, late I_{Na}-dependent Na overload leads to intracellular Ca accumulation either by reduced Ca exit due to limitations to Ca extrusion by NCX or by additional Ca entry via reverse mode NCX.[15] Intracellular Ca accumulation is associated with increased diastolic SR Ca leak and DADs (Figure 5). Moreover, it contributes to diastolic dysfunction in HF and under conditions of increased ROS production,[15,89] and it may even lead to cellular hypercontracture.[95]

AP-clamp experiments revealed that late I_{Na}-dependent Na entry also substantially contributes to arrhythmias in LQT3 syndrome.[96] Consistent with this evidence, blocking late I_{Na} and Ca entry via NCX have been shown to inhibit afterdepolarizations.[23,97]

What are the mechanisms that lead to increased late I_{Na}? ROS have been shown to increase $[Na]_i$, prolong APD and induce EADs, and ROS-enhanced late I_{Na} may be involved.[15,23,90] Ahern and colleagues showed that nitrosylation of $Na_V1.5$ increased late I_{Na} under physiologic and pathophysiologic conditions.[98] Over recent years, however, a body of evidence suggests that CaMKII associates with and phosphorylates $Na_V1.5$ leading to increased late Na current, and some ROS and nitric oxide effects may be mediated via CaMKII activation (Figure 6).[14,15,57,99–103]

Since late I_{Na} is strongly linked to cardiac arrythmogenesis, strategies aimed at inhibiting late I_{Na} may have strong anti-arrhythmic potential and may possibly be used to prevent SCD. The clinically approved anti-anginal drug ranolazine was found to inhibit late

I_{Na}.[104,105] Within the therapeutic range, which varies between 2 and 8 μmol/L, ranolazine also inhibits I_{Ca} by 30%, which could limit Ca entry,[105] and I_{Kr}, which can prolong APD. Depending of the actual ionic conditions, the effects of ranolazine on APD may vary. Inhibition of late I_{Na} by ranolazine has been shown, for instance, to reduce ROS-dependent AP prolongation, as well as intracellular Na and Ca accumulation, diastolic dysfunction and arrhythmias.[15,23,88,106,107] Ranolazine has been demonstrated to inhibit afterdepolarizations, to reduce transmural dispersion of repolarization and to inhibit spatially discordant repolarization alternans in various models of enhanced late I_{Na}.[94,104,105,108–110] It also prevented pacing-induced reentry and multifocal ventricular fibrillation.[111] In experimental models of systolic HF, ranolazine treatment also improved systolic function[112] possibly by reducing late I_{Na}-dependent diastolic SR Ca leak.[18]

The clinical safety and efficacy of ranolazine are well investigated. A large clinical outcome trial investigating the efficacy of ranolazine to reduce cardiovascular death, myocardial infarction or recurrent ischemia in more than 6000 patients with acute coronary syndrome (MERLIN-TIMI-36) was not able to show an improvement in outcome.[113] Nevertheless, subgroup analysis revealed that in placebo treated patients prolonged QTc was a significant independent predictor for SCD, while this was not the case in patients treated with ranolazine,[114] suggesting a potential beneficial effect in the prevention of SCD. Investigation of the seven-day Holter monitoring data acquired in the MERLIN-TIMI-36 trial revealed a reduction in the incidence of ventricular tachycardia in the ranolazine treated patients.[115] Ranolazine also reduced VT burden and ICD shocks in a small observational study of patients with refractory VT and previous ICD shocks.[116] In a small study of patients with long QT syndrome 3, ranolazine shortened the QTc interval in a concentration-dependent manner.[117] Moreover, in patients with atrial fibrillation (AF) a dose-finding randomized controlled trial (RAFFAELLO) showed a decreased rate of in overall AF recurrence.[118]

CaMKII

CaMKII is a central regulator of many Na and Ca (and K) channels and transporters. It is well established that transgenic overexpression of CaMKII results in the development of HF and arrhythmias,[14,119] and that CaMKII inhibition prevented afterdepolarizations and arrhythmias upon β-adrenergic stimulation.[17]

Increased CaMKII autophoshorylation was observed in rabbit chronic atrioventricular block models of left ventricular dysfunction, acquired long QT syndrome and incessant ventricular tachycardia.[120,121] In addition, CaMKII inhibition prevents the development of structural heart disease or arrhythmias upon myocardial infarction,[122] increased ROS formation,[15] pressure overload,[123] or pacing-induced incessant VT.[121] Calcineurin overexpressing mice with increased CaMKII activity show contractile dysfunction and arrhythmias.[124] Also here, CaMKII inhibition improved contractile function and suppressed arrhythmias.[124]

Oxidized CaMKII has been shown to be involved in ROS-induced enhancement of late I_{Na} (Figure 6) leading to intracellular Na and Ca accumulation, contractile dysfunction and triggered activity.[15,125] Increased oxidative activation of CaMKII due to enhanced NADPH oxidase 2 may also be important for angiotensin II-dependent arrhythmogenesis.[126,127]

Moreover, oxidized CaMKII plays a role in diabetes-dependent increased mortality after myocardial infarction possibly by sinus node dysfunction.[128] A novel CaMKII activation pathway by O-linked glycosylation at serine 279 was demonstrated during acute hyperglycemia. This activation confers similar autonomous activity as autophosphorylation or oxidation.[129] O-linked glycosylation upon diabetic hyperglycemia was shown to result in increased diastolic SR Ca leak and be pro-arrhythmogenic.[129] CaMKII can be also nitrosylated at another site in the regulatory domain to cause autonomous activation.[130] Nitrosylation-dependent CaMKII activation has been implicated in increased SR Ca leak in cardiac myocytes.[131,132] Neurohumoral activation that occurs in HF has been shown to activate CaMKII. Both β-adrenergic stimulation and angiotensin II exposure can activate CaMKII either by increased cytosolic Ca or ROS.[11,122, 126,133–136]

The mechanisms of CaMKII dependent arrhythmias are complex, since CaMKII regulates a variety of ion channels and transporters (Figure 6). CaMKII was first identified to increase peak L-type Ca current and slow I_{Ca} inactivation,[137–139] which may predispose to EADs.[140–142]

CaMKII is also known to associate with and phosphorylate cardiac $Na_V1.5$.[14,15,57,99–103] Beside increased late I_{Na} that may contribute to AP prolongation, increased EAD and DAD formation and repolarization alternans, CaMKII-dependent phosphorylation also enhanced I_{Na} intermediate inactivation and slowed recovery from inactivation.[14,57,102,103] Both effects reduce the steady-state availability of I_{Na}, which could lead to repolarization alternans at high heart rates. Reduced Na channel availability can also increase transmural dispersion of repolarization and slow intra-ventricular conduction (Figure 7).[14] This peculiar phenotype of CaMKII-dependent gain in Na channel function (enhanced late I_{Na}) and loss of Na channel function (reduced I_{Na} availability) may sound incongruous. However, similar changes in I_{Na} gating have been observed in a *SCN5A* mutation (1795InsD) associated with features of both Brugada and long QT syndrome.[143,144] Thus, increased CaMKII activity in HF may lead to an acquired from of combined long QT and Brugada syndrome.

There is an overwhelming body of evidence that CaMKII regulates RyR2 and SERCA2a. While RyR2 is directly phosphorylated at serine 2814,[145] the activity of SERCA2a is indirectly influenced by phosphorylation of phospholamban (PLN) at threonine 17. The latter results in relief of PLN-dependent SERCA2a inhibition and activation of SERCA2a.[146] In HF, increased diastolic Ca leak through RyR2 occurs in the face of a reduced SR Ca reuptake due to a smaller SERCA2a/PLN expression ratio. This results in a reduced SR Ca content, which is an important determinant for the impaired Ca transient amplitude of failing cardiomyocytes.[6,147,148] In HF CaMKII-dependent diastolic SR Ca leak is a major cause for DADs by activating forward mode NCX.[149,150]

Zhang *et al.*[151] tried to rescue cardiac function in $CaMKII\delta_C$ transgenic with reduced SR Ca load by PLN ablation. While this improved SR Ca load and Ca transients, this occurred at the expense of increased CaMKII-dependent SR Ca leak, mitochondrial Ca loading and myocyte death. Thus despite improved myocyte function, cardiac function, HF progression and mortality were worsened by the PLN ablation.

More insights into the role of CaMKII-dependent SR Ca leak for contractile dysfunction and arrhythmias in HF comes from animal models with increased afterload or myocardial infarction. It was shown that afterload induced HF development and arrhythmias were inhibited in knock-in mice harboring only a mutant RyR2 (S2814A) that cannot be phosphorylated by CaMKII at that site.[152,153] This knock-in however, did not prevent HF post-myocardial infarction.[152] In contrast, recent data show similar CaMKII-dependent SR Ca leak in isolated human ventricular cardiomyocytes from ischemic and dilated cardiomyopathy.[154]

Also, KI mice with a CaMKII-phosphomimetic mutation (S2814D) exhibited increased SR Ca leak and developed sustained ventricular tachycardia and SCD upon β-adrenergic stimulation, programmed electrical stimulation and increased afterload.[153] This sort of CaMKII-dependent SR Ca leak has also been observed upon β-adrenergic stimulation,[155–157] and by activation of NADPH oxidase resulting in DADs.[126] While much attention has been on ventricular muscle, it was also shown that CaMKII-dependent SR Ca leak is crucially involved in atrial arrhythmo-genesis.[158–161] For ROS-induced SR Ca leak, however, a direct oxidation of the RyR2 has also been proposed.[15,162–164] Thus, CaMKII inhibition may be a novel strategy to prevent SCD.

Catecholaminergic polymorphic ventricular tachycardia

Increased SR Ca leak is causally involved in catecholaminergic polymorphic ventricular tachycardia (CPVT), a rare familial condition characterized by ventricular arrhythmias that are associated with exercise or catecholaminergic stimulation in a structurally normal heart.[165] CPVT occurs at young ages. For example the majority of 101 patients with CPVT had symptoms before the age of 21.[166] Importantly, CPVT accounts for 15% of all sudden unexplained deaths in young people. CPVT is linked to mutations in *RyR2* and the intra-SR Ca binding and RyR2-associated proteins calsequestrin (*CASQ2*) and triadin (*TRND)*.[167–171] For a substantial fraction of patients, however, the disease-causing gene has remained elusive to date. As a result of the irregular SR Ca release[172] electrogenic NCX is activated causing DADs. Clinically, patients exhibit monomorphic ventricular premature beats and more severe bidirectional ventricular tachycardia, which can degenerate into polymorphic VT and VF. Interestingly, pharmacological CaMKII inhibition has recently been shown to inhibit stress-induced arrhythmias and triggered activity in a mouse model of CPVT (RyR2 R4496C$^{+/-}$).[173] The opposite, transgenic CaMKII overexpression in RyR2 R4496C$^{+/-}$ mice resulted in increase SR Ca leak, DADs, arrhythmias upon β-adrenergic stimulation, and increased mortality possibly due to SCD.[174] Since disturbed CaMKII-dependent regulation of SR Ca release is a frequent feature of HF, exercise-induced arrhythmias in HF may be related to the same underlying mechanism. For more information about this important genetic arrhythmogenic disease the reader is referred to these more comprehensive reviews.[175–177]

Epigenetic modifications related to SCD

Epigenetic regulation of gene expression is increasingly recognized as important contributor arrhythmias.[178] This is an emerging area includes microRNAs, DNA methylation and

histone modifications (e.g. acetylation/deacetylation). Apropos to the Ca/CaMKII focus here, it is known that CaMKII can importantly influence the nuclear export of class II histone deacetylases (e.g. HDAC4 and HDAC5) and that that can modulate transcription of key proteins involved in hypertrophic signaling and arrhythmias.[179–181] CaMKII can also directly phosphorylate histone H3 and contribute to hypertrophic changes in gene expression.[182,183] Thus, CaMKII seems to be integrally involved in epigenetic mechanisms of cardiac hypertrophy, and some of tha consequent changes in protein expression (of ion channels and Ca regulatory proteins) may also contribute to enhanced propensity for arrhythmias.

Conclusions

Cardiac myocyte Na and Ca fluxes and concentrations are tightly controlled, but also change dynamically as part of normal physiological modulation of cardiac electrical, contractile and energetic state. There is very tight coupling between Na, Ca, electrical, mechanical and energetic properties in the heart, only some of which we touched upon here. Many arrhythmias are a result of dysregulation of this complex system. To understand how deranged Na and Ca homeostasis comes about in pathophysiological states and how it contributes to electrical and contractile dysfunction such as HF, arrhythmias and SCD is a challenge. But this understanding is essential for progress in novel therapeutic approaches to these major clinical problems.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Non-standard Abbreviations and Acronyms

AP	action potential
APD	action potential duration
CaMKII	Ca/Calmodulin-dependent protein kinase
II CPVT	catecholaminergic polymorphic ventricular tachycardia
CV	conduction velocity
DAD	delyed afterdepolarization
EAD	early afterdepolarization

HF	heart failure
ICD	implantable cardioverter-defibrillators
I_f	hyperpolarization-activated non-specific cation current
I_{K1}	inward rectifying K current
I_{Kr}	rapid activating delayed rectifying K current
I_{Ks}	slowly activating delayed rectifiying K current
I_{Na}	Na current
I_{NaK}	Na/K-ATPase current
I_{NCX}	Na/Ca exchange current
I_{TI}	transient inward current
I_{to}	transient outward potassium current
LQT	long QT syndrome
LTCC	L-type Ca channels
MCU	mitochondrial Ca uniporter
MERLIN-TIMI-36 trial	Metabolic Efficiency With Ranolazine for Less Ischemia in Non ST-Elevation Acute Coronary Syndrome Thrombolysis in Myocardial Infarction 36 trial
NCX1	Na/Ca-exchanger 1
PLN	phospholamban
PMCA	sarcolemmal Ca ATPase
RAFFAELLO trial	Ranolazine in Atrial Fibrillation Following An ELectricaL CardiOversion trial
ROS	reactive oxygen species
RyR2	cardiac ryanodine receptor 2
SCD	sudden cardiac death
SERCA2a	SR Ca ATPase 2a
SR	sarcoplasmic reticulum
TWA	T wave alternans
VF	ventricular fibrillation
V_m	membrane potential
VT	ventricular tachycardia

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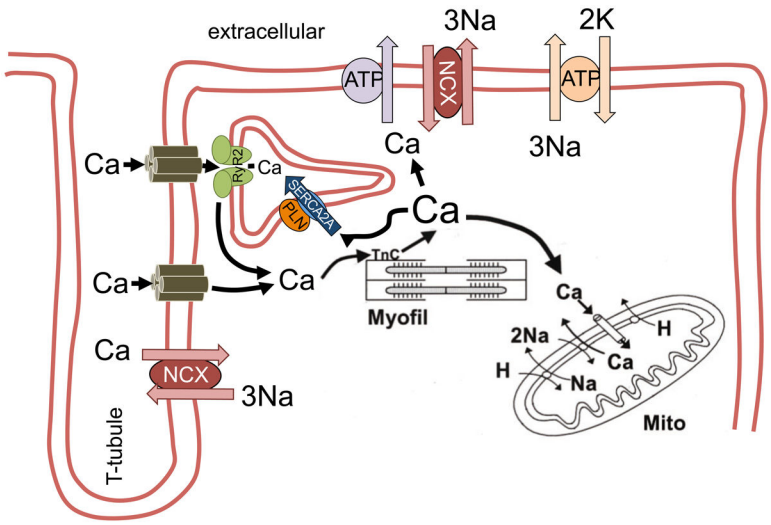

Figure 1.

Schematic diagram of cellular Ca fluxes during excitation-contraction coupling. Ca entry via L-type Ca channels triggers Ca-induced Ca release from the sarcoplasmic reticulum (SR), which results in myofilament activation. For relaxation, cytosolic Ca is transported into the SR via SR Ca-ATPase (SERCA2a) and into the extracellular space via sarcolemmal Na/Ca exchanger. Reproduced with permission from the AHA.[184]

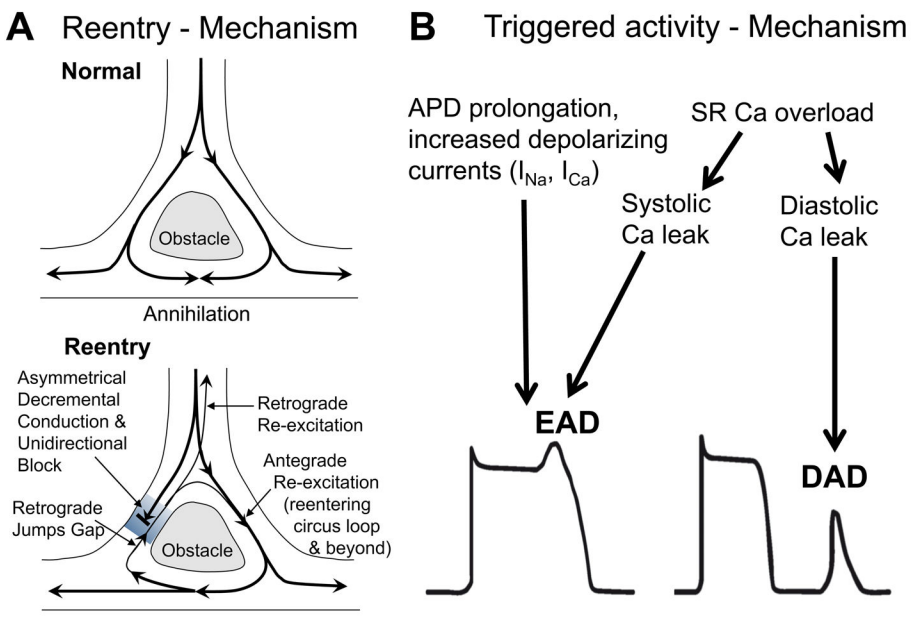

Figure 2.

Proarrhythmogenic mechanisms. A) Reentry. Upper panel shows normal conduction around an obstacle. The latter exhibits electrical properties that differ dramatically from the rest of the myocardium (slowed conduction and/or repolarization). The wavefront propagates around this line of block and reaches the back from multiple directions simultaneously resulting in wave annihilation. If, however, unidirectional block (often coupled with decremental conduction) exists around one side (lower panel), the wavefront can reenter and re-excite tissue in front of the unidirectional block. This can lead to stable reentry. B) Triggered activity. Increased depolarizing currents that result in prolongation of action potential duration (APD) can favour L-type Ca channel reactivation. Increased Ca entry via I_{Ca} can also lead to SR Ca overload and spontaneous SR Ca release during AP plateau phase. This may generate transient inward (I_{Ti}) current by Na/Ca exchange. Both Ca channel reactivation and I_{Ti} may depolarize the membrane during AP plateau phase, which can result in an early afterdepolarization (EAD). In addition, SR Ca overload may also result in diastolic SR Ca release. The consequent I_{Ti} may lead to depolarization from the resting membrane potential, which can result in a delayed afterdepolarization (DAD). Partially reproduced.[31]

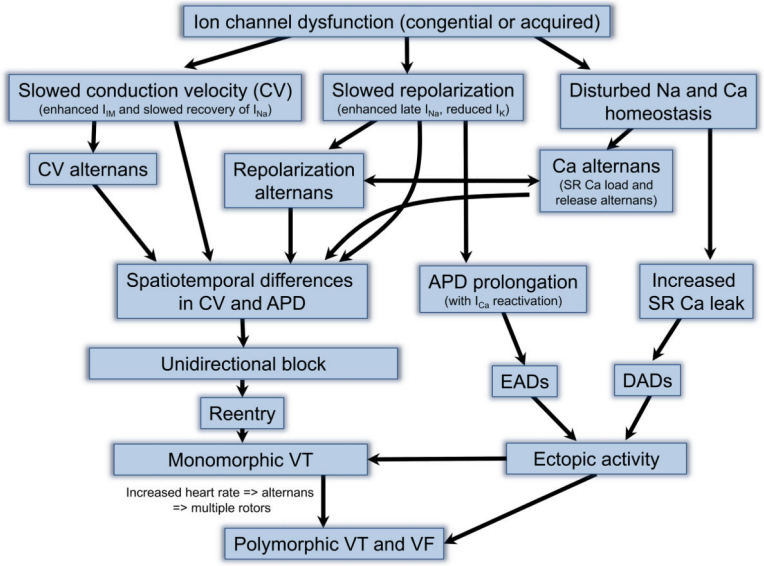

Figure 3.

Overview of proarrhythmic consequences of ion channel dysfunction. Congenital or acquired dysfunction of ion channels can result in 1) slowed conduction, 2) repolarization and/or 3) disturbed intracellular Na and Ca homeostatis. Slowed conduction velocity (CV; with or without CV alternans) or repolarization (with or without repolarization alternans) causes spatiotemporal differences in CV and action potential duration (APD) within the myocardium. These regional differences can lead to unidirectional block with reentry and rotor formation. The consequent monomorphic ventricular tachycardia (VT) may result in additional rotors by heart rate-dependent alternans causing polymorphic VT and ventricular fibrillation (VF). Disturbed Na and Ca homeostasis, on the other hand, may lead to Ca alternans, which is linked to repolarization alternans. Moreover, prolongation in APD duration causes EADs and increased Ca leak results in DADs, both of which underlie ectopic activity. The latter can also lead to monomorphic of polymorphic VT and VF.

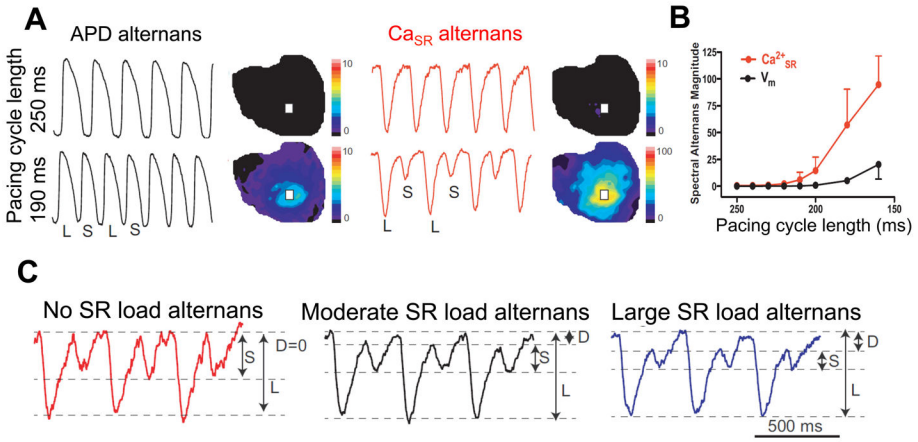

Figure 4.

Characteristics of cardiac alternans. A) Simultaneous recordings of AP and intra-SR free [Ca] in isolated Langendorff-perfused rabbit hearts by optical mapping. At shorter pacing intervals (190 ms), alternans of the AP duration as well as SR Ca release alternans was observed. B) SR Ca release alternans can occur at heart rates where APD alternans is not yet detectable. C) Ca release alternans can be amplified by alternating changes in SR Ca load, i.e. SR Ca load alternans. Data reproduced with permission.[43]

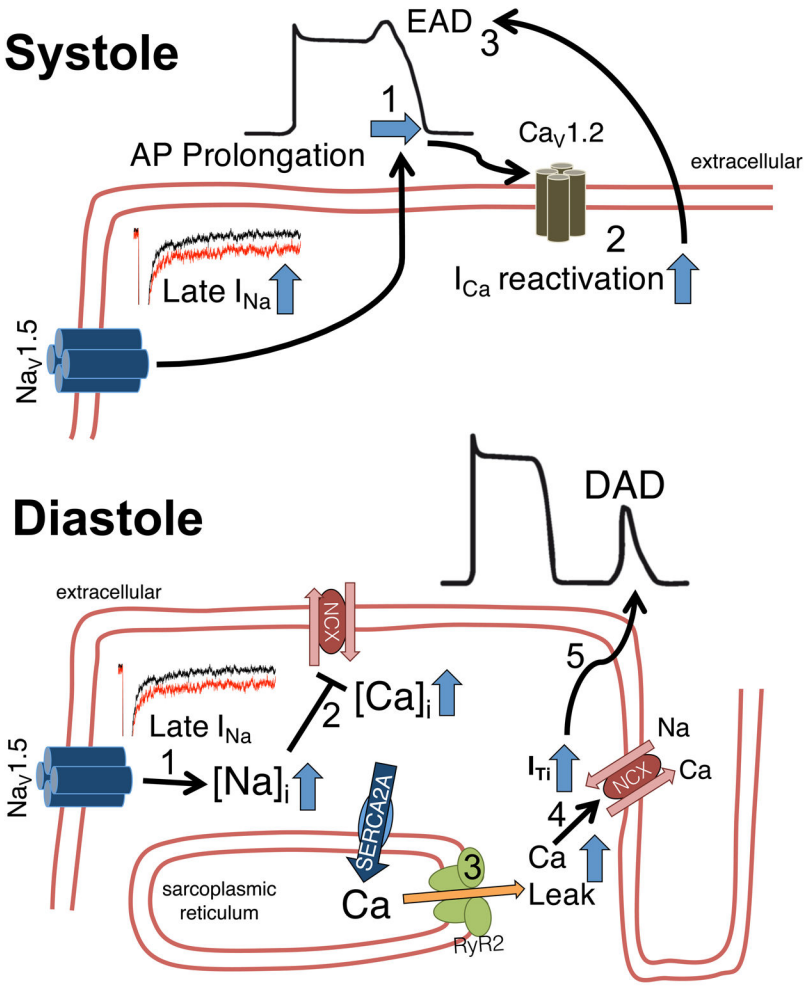

Figure 5.

Proarrhythmogenic mechanisms of enhanced late I_{Na}. In systole (upper panel), enhanced late I_{Na} leads to AP prolongation (1). The longer AP plateau phase increases the likelihood of I_{Ca} reactivation (2), which may lead to early afterdepolarizations (EAD, 3). Lower panel: The increased amount of Na influx also results in increased intracellular Na (1), which impairs Ca elimination (2) by the Na/Ca exchanger (either less forward or even increased reverse mode activity). In diastole, the increased intracellular Ca facilitates SR Ca leak (3), which could lead to transient inward current (I_{Ti}) by the Na/Ca exchanger (4). The latter can result in delayed afterdepolarizations (DAD, 5).

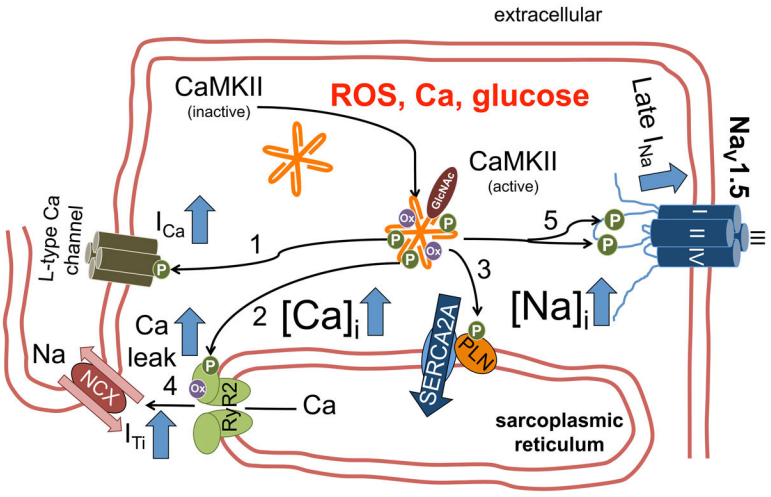

Figure 6.

CaMKII-dependent mechanisms of triggered activity. CaMKII is activated by pathophysiologically relevant stimuli, i.e. increased reactive oxygen species (ROS), increased intracellular Ca, hyperglycemia. CaMKII-dependent phosphorylation of L-type Ca channels (1) may increase I_{Ca} window current predisposing to EADs. Increased CaMKII-dependent RyR2 phosphorylation (2) results in increased diastolic Ca leak. CaMKII-dependent phospholamban (PLN) phosphorylation (3) maintains SR Ca content, which may also stimulate diastolic RyR2 openings from the luminal side. Diastolic SR Ca release triggers transient inward current (I_{Ti}, 4) and DADs. Increased CaMKII-dependent phosphorylation of $Na_V1.5$ (5) leads to enhanced late I_{Na}, which predisposes for both EADs and DADs (Figure 5).

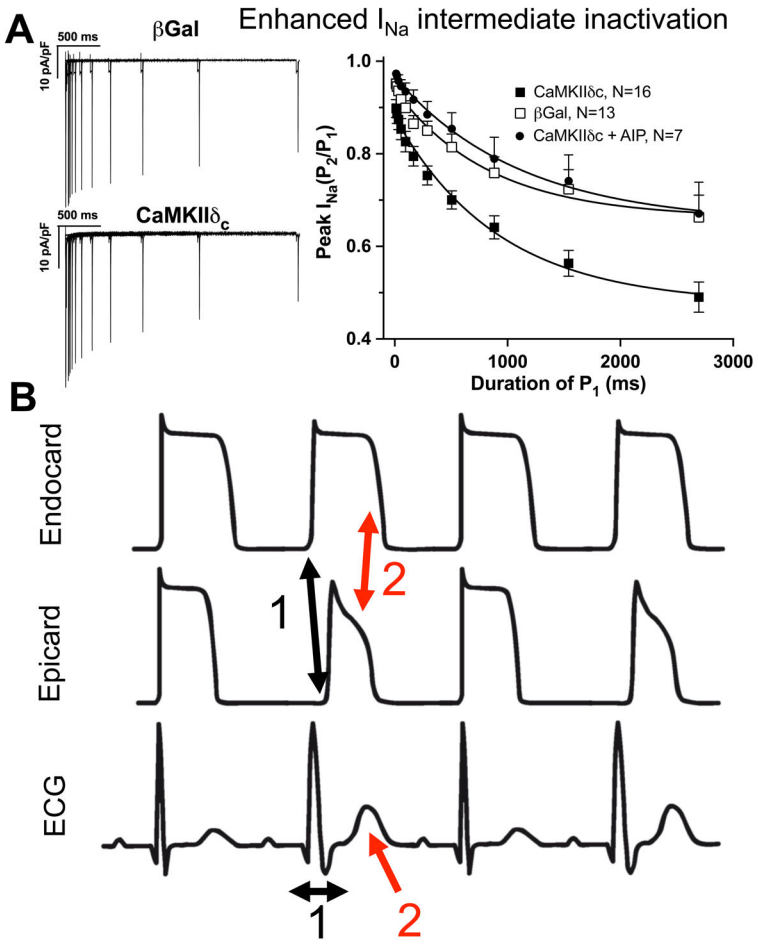

Figure 7.

CaMKII-dependent regulation of I_{Na} gating and alternans. A) CaMKII-dependent phosphorylation of $Na_V1.5$ has been shown to enhance I_{Na} intermediate inactivation (reproduced from Wagner et al[14] with permission; whole-cell patch clamp in rabbit ventricular myocytes). As a result, the number of available Na channels is reduced especially at shorter diastolic intervals. B) Consequences of enhanced I_{Na} intermediate inactivation: CV and repolarization alternans. Reduced Na channel availability results in slowed intramural conduction and slowed AP upstroke velocity (1) evident as broader QRS complex on surface ecg (1). In addition, K channel expression is larger in epicardium. Therefore, repolarization is faster in epicardium, especially if Na current is reduced (2). This leads to increased transmural dispersion of repolarization evident as larger and wider T wave on surface ecg (2). Interestingly, Na channels in intermediate inactive state cannot be activated (and become refractory) during the excitation. Thus, these channels are available for the consecutive excitation. Consequently, conduction velocity and AP upstroke velocity will be larger, AP duration longer for the consecutive excitation: the typical pattern of CV and repolarization alternans.