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Cardiac metabolism and arrhythmias

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Abstract

Sudden cardiac death remains a leading cause of mortality in the Western world, accounting for up to 20% of all deaths in the U.S.^{1, 2} The major causes of sudden cardiac death in adults age 35 and older are coronary artery disease (70–80%) and dilated cardiomyopathy (10–15%).³ At the molecular level, a wide variety of mechanisms contribute to arrhythmias that cause sudden cardiac death, ranging from genetic predisposition (rare mutations and common polymorphisms in ion channels and structural proteins) to acquired electrophysiological and structural remodeling in left ventricular hypertrophy and failure.^{4, 5} A growing body of evidence suggests that altered ion channel function is closely linked to changes in metabolic activity in a wide variety of pathological conditions. In this review we focus on the mechanisms by which altered metabolic function impacts cardiac electrophysiology. We will review the specific molecular targets that allow cardiomyocytes to recognize alterations in their metabolic state and translate this information into changes in membrane excitability in various pathophysiological conditions including ischemia-reperfusion, heart failure (HF), left ventricular hypertrophy, diabetic cardiomyopathy and atrial fibrillation. A comprehensive understanding of the interrelated processes of metabolic and electrical remodeling promises to identify new molecular targets for the treatment of cardiac arrhythmias.

Keywords

Metabolism; Ischemia; Diabetes mellitus; Arrhythmia; Ion channels

1. Maintenance of sodium and calcium homeostasis is critical for electrical stability

Free energy released from the hydrolysis of high-energy phosphates is essential for maintenance of cellular homeostasis. Maintenance of Na⁺ and K⁺ gradients across the plasma membrane is among the most energy-intensive cellular processes in the heart. Ultimately, all transmembrane ionic movements are driven by the free energy released from ATP hydrolysis by P-type (P for phosphorylated intermediate) ATPases, including the Na⁺-K⁺-ATPase and the sarcoplasmic reticulum Ca²⁺-ATPase. The electrochemical gradient generated by the Na⁺-K⁺-ATPase establishes the gradients of Na⁺ and K⁺ across the sarcolemma, thus establishing the driving force for the passage of these ions across the myocyte cell membrane through voltage-dependent ion selective channels. The energy stored in the electrochemical

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Na⁺ gradient is used to move other ions across the sarcolemma. For instance, it provides the driving force for Ca²⁺ removal from the cytoplasm to the extracellular space via the Na⁺-Ca²⁺-exchanger (NCX1 encoded by *SLC8A1*). Removal of Ca²⁺ during diastole is also achieved through a second P-type ATPase located in the sarcoplasmic reticulum membrane (SERCA2 encoded by *ATP2A2*) which transports Ca²⁺ from the cytosol of the cell to the lumen of the sarcoplasmic reticulum (SR) at the expense of ATP hydrolysis during muscle relaxation.

Under physiological conditions, ATP is mainly supplied by mitochondrial oxidative phosphorylation and to a lesser degree by glycolysis. Commensurate with the large metabolic demand of contraction of the heart, mitochondria occupy approximately 30% of the volume of ventricular cardiomyocytes⁶ and form a network around the myofilaments, thus placing the sites of ATP production immediately adjacent to the sites of ATP consumption.⁷ The critical dependence of the ion homeostasis on sufficient energy supply becomes evident in pathophysiological conditions as diverse as ischemia/reperfusion, HF and ventricular hypertrophy, where a mismatch in ATP supply and ATP utilization may lead to electrical and mechanical instability.

During severe ischemia, for instance, oxidative metabolism comes to a halt. Even though anaerobic glycolysis increases in a compensatory fashion, this process is unable to supply sufficient amounts of ATP to maintain long-term viability and function. As a consequence, concentrations of ATP may fall by more than 70% within 20min after onset of ischemia,⁸ thereby limiting the function of the Na⁺-K⁺-ATPase, reducing the extrusion of sodium ions and dissipating the transmembrane ion and voltage gradients. Anaerobic glycolysis may further aggravate intracellular sodium loading, as accumulating protons (generated from lactate) activate the Na⁺-H⁺-exchanger (NHE1 encoded by *SLC9A1*) which exchanges intracellular H⁺ for extracellular Na⁺. Metabolic inhibition, as observed in ischemia, also promotes opening of connexin-43 hemichannels. Connexin proteins are assembled together in groups of six to form hemichannels (or connexons) which can either combine end-to-end to form gap junction channels or occur as single connexons in non-junctional regions. If activated in the nonjunctional plasma membrane by metabolic inhibition, hemichannels are non-selective cation channels and permit K⁺, Na⁺ and Ca²⁺ to move down their respective electrochemical gradients across the sarcolemma.^{9, 10} Based on their large unitary conductance (120pS) and high open probability, evidence suggests that only a small number of open connexin-43 hemichannels is sufficient to double the Na⁺ influx of a normal beating myocyte.^{10, 11} The notion that intracellular sodium ([Na⁺]_i) overload contributes to electrical instability is supported by the fact that high [Na⁺]_i has been found to be a strong predictor of ventricular fibrillation (VF) in experimental models of myocardial ischemia.¹² In addition to ischemia, profound metabolic abnormalities with elevation of [Na⁺]_i are also encountered in pathophysiological states as diverse as left ventricular hypertrophy, HF or diabetes mellitus – all of which are associated with an increased incidence of arrhythmias.^{13–15} In diabetes, it has been shown that hyperglycemia directly inhibits the Na⁺-K⁺-ATPase,¹⁶ thus promoting intracellular Na⁺ overload. In left ventricular hypertrophy and HF, a rise in [Na⁺]_i may partially compensate for depressed contractility by raising cytosolic Ca²⁺ via the reverse-mode NCX1-current.

Intracellular Na⁺ loading is linked to arrhythmias by a number of mechanisms, as summarized in Figure 1: First, intracellular Na⁺ accumulation leads to net K⁺ loss because of the need to maintain electroneutrality and osmotic balance.¹⁷ Accumulation of extracellular K⁺ not only promotes diastolic injury currents which trigger extrasystoles, but also progressively slows conduction and alters refractoriness, generating both the trigger and substrate for reentry.¹⁸ Second, elevation of [Na⁺]_i may further exacerbate a mitochondrial energetic deficit, observed in various pathophysiological states. Recent evidence suggests that cardiac mitochondria take up Ca²⁺ rapidly via the Ca²⁺ uniporter (MCU).¹⁹ Under physiological conditions, the extrusion

rate of mitochondrial calcium from the mitochondrial matrix via the mitochondrial sodium-calcium exchanger (mNCX) is slower than the mitochondrial Ca^{2+} uptake,^{19, 20} so that, at higher heart rates, Ca^{2+} accumulates in the mitochondrial matrix, activating several enzymes of the tricarboxylic acid (TCA) cycle and increasing NADH production. Together with the high-energy phosphotransfer enzymes creatine kinase (CK) and adenylate kinase (AK), mitochondrial Ca^{2+} accumulation thereby facilitates the matching of NADH/NAD⁺ redox potential to ATP production in periods of increased energetic demand.²¹ The balance between mitochondrial uptake and release of Ca^{2+} can be modified by a variety of factors, including mitochondrial inorganic phosphate, ADP and also $[\text{Na}^+]_i$.^{22, 23} In conditions where cytosolic Na^+ is elevated, the decay rate of the mitochondrial calcium transient is increased and mitochondrial Ca^{2+} accumulation is impaired as more calcium is extruded via the mitochondrial NCX.^{19, 22} Consequently, high intracellular Na^+ will lead to a vicious cycle exacerbating the mismatch between ATP demand and ATP supply, as the reduction of Ca^{2+} in the mitochondrial matrix leads to NADH oxidation.¹⁹

Finally, elevation of $[\text{Na}^+]_i$ in myocardial ischemia and reperfusion activates reverse-mode Na^+ - Ca^{2+} -exchanger, thereby promoting intracellular calcium overload, as the cell exchanges three sodium ions for one calcium ion.

2. Metabolic alterations of calcium homeostasis and excitation-contraction coupling

Following the rapid depolarization of the action potential, Ca^{2+} enters the cell via L-type calcium channels ($I_{\text{Ca,L}}$) and triggers calcium-induced calcium release from the sarcoplasmic reticulum. During metabolic inhibition, multiple studies have documented a reduction of the amplitude of $I_{\text{Ca,L}}$ in ventricular myocytes of guinea pigs,^{24, 25} rats²⁶ and rabbits,^{27, 28} thought to have important functional consequences: First, the reduction in $I_{\text{Ca,L}}$ contributes to shortening of the action potential (AP) duration during ischemia together with activation of sarcolemmal K_{ATP} channels (see section 4). However, the overall contribution of $I_{\text{Ca,L}}$ to shortening of the AP during ischemia is still a matter of debate, as Verkerk and colleagues have demonstrated that $I_{\text{K}_{\text{ATP}}}$ - induced AP shortening occurred independent of changes in $I_{\text{Ca,L}}$.²⁹ Second, reduction in $I_{\text{Ca,L}}$ amplitude will decrease the calcium-induced calcium release from the sarcoplasmic reticulum. Metabolic inhibition, intracellular acidification, a reduction in ATP and a rise in ADP concentrations will increase the cytoplasmic free calcium ($[\text{Ca}^{2+}]_i$)³⁰ and inhibit both the SR Ca^{2+} uptake (via SERCA2)³¹ and the SR Ca^{2+} release (via the ryanodine receptor RyR2),^{31–33} thus, the net effect on the calcium transient is complex and multifactorial. Overall, in ischemia the reduction in SR Ca^{2+} release appears to predominate over the reduction in SR Ca^{2+} uptake, manifest as a decrease in the frequency of spontaneous release of Ca^{2+} via RyR2³¹ and a marked decrease in the area of the cell exhibiting organized Ca^{2+} release.³⁴ Consequently, SR Ca^{2+} content tends to increase during metabolic stress and ischemia.³¹ Upon reperfusion, removal of the inhibitory effect on RyR2 could give rise to spontaneous, arrhythmogenic waves of Ca^{2+} release. Perhaps more importantly, these complex alterations in subcellular Ca^{2+} handling have been implicated in the genesis of calcium transient (CaT) alternans which can give rise to AP- or T-wave alternans, preceding VF.^{35–37} Of note, at physiological pacing frequencies, neither CaT nor AP alternans are observed in normally perfused myocardium, but occur exclusively in the ischemic area or the border zone after 2 to 4 minutes of ischemia.³⁸ Consequently, the spatial heterogeneity of the CaT during the early phase of ischemia could produce electrical instability and arrhythmias.³⁵

In HF, it is well established that altered functional expression of SERCA2 plays an important role in the abnormal Ca^{2+} homeostasis, however the mechanisms underlying SERCA2 dysregulation are not fully understood. Using a genome-wide transcriptional approach in a canine tachypacing HF model, we demonstrated that changes in SERCA2 mRNA occurred as

early as 3 days after initiation of tachypacing and were accompanied by concomitant prolongation of the AP.³⁹ What is more, about half of the transcripts associated with SERCA2 expression (18 out of 37) were directly linked to oxidative phosphorylation, ATP synthesis, fatty acid β -oxidation, and the TCA cycle.³⁹ This suggests a coordinate dysregulation shared by SERCA2 and energetic pathways during tachypacing-induced HF. To our knowledge, this was the first report linking changes in AP duration and SERCA2 mRNA transcript levels to metabolic activity in left ventricular dysfunction. Importantly, the close transcriptional correlation between mitochondrial genes and SERCA2 is not confined to the pacing-induced HF model, but is also observed in mouse myocardium (Figure 2) and human HF (e.g. Gene Expression Omnibus accession number GSE5406). Recent data showing that the mitochondrial transcription factors Tfam and Tfb2m⁴⁰ bind to the SERCA2 promoter and regulate SERCA2 transcript levels, provide first mechanistic insights into the coordinate regulation of ATP production and expenditure in mammalian myocardium.⁴¹

3. Metabolic activity alters expression and function of repolarizing potassium currents

Besides regulating intracellular Na^+ and Ca^{2+} homeostasis, metabolic activity has also been shown to critically affect repolarizing K^+ currents. Other than K_{ATP} , one of the first K^+ channels recognized to be modulated by metabolic inhibition was the Ca^{2+} -independent transient outward K^+ current, I_{to} . Inhibition of oxidative phosphorylation, using inhibitors such as 2,4-dinitrophenol (DNP) and cyanide, markedly decreased the magnitude of the 4-AP sensitive I_{to} .⁴² Remodeling of cardiac I_{to} has also been implicated in diabetes mellitus, one of the leading metabolic abnormalities associated with arrhythmias. Compared to healthy individuals, diabetic patients show a higher incidence of AF, VF and sudden cardiac death.^{14, 43} Electrocardiographically, diabetic patients often display QT-interval prolongation and T wave abnormalities.¹⁴ Studies designed to elucidate the cellular mechanisms of diabetes-induced repolarization abnormalities have consistently demonstrated AP prolongation in myocytes isolated from diabetic animals. This was mainly due to a net decrease in outward repolarizing currents, including I_{to} .^{44–46} A primary role of metabolic changes in regulation of I_{to} is suggested since down regulation of I_{to} in cardiomyocytes from diabetic hearts could be reversed by short-term treatment with insulin.⁴⁴ Recent studies have shed some light on the mechanisms by which diabetes mellitus alters the functional expression of cardiac ion channels. Peroxisome proliferator-activated receptor alpha ($\text{PPAR}\alpha$), a key regulator of fatty acid and glucose metabolism is up regulated in diabetic hearts and has been found to lead to remodeling of a wide variety of ion channels, most prominently I_{to} .⁴⁷ Transgenic mice with chronic, cardiac-specific activation of $\text{PPAR}\alpha$ displayed decreased I_{to} density, concomitant with reduced protein expression of the alpha ($\text{Kv}4.2$) and beta (KChIP2) subunits of I_{to} channels.⁴⁷ In contrast, transgenic animals with deletion of the $\text{PPAR}\alpha$ -gene, showed increased density of I_{to} .⁴⁷ Of note, in $\text{PPAR}\alpha$ -overexpressing animals, these changes occurred well before any signs of LV hypertrophy or LV dysfunction became apparent, suggesting that altered metabolic activity directly affects expression of I_{to} . In addition to up regulation of $\text{PPAR}\alpha$, a rise in plasma free fatty acids in diabetes mellitus increases the rate of β -oxidation. Amphiphilic fatty acid metabolites, such as palmitoylcarnitine and palmitoyl-CoA have been shown to directly suppress I_{to} in rodents.⁴⁸ Activation of neurohormonal systems, including the renin-angiotensin-system, also contribute to potassium channel remodeling in the diabetic heart.⁴⁹ Likewise, diabetes-induced down regulation of I_{to} involves the formation of reactive oxygen species (ROS) and incubation of cells isolated from diabetic hearts with reduced glutathione (GSH) was able to reverse down regulation of I_{to} .⁴⁴

While most of these studies have been carried out in rodents, recent studies demonstrate that diabetes-induced remodeling of potassium channels also holds true for larger mammals, which share a far greater similarity of ventricular repolarization to humans. In dogs, for instance,

diabetes-induced repolarization abnormalities were associated with prominent down regulation of I_{to} .⁵⁰ In addition, a decrease in the density of the slow component of the delayed rectifier current I_{Ks} , and a reduction in protein levels of the beta-subunit, minK (encoded by *KCNE1*) were observed.⁵⁰ Functional down regulation of potassium channel subunits and currents can be regarded as acquired long QT syndrome whereby the reduced repolarization reserve increases the predisposition to early afterdepolarizations, triggered arrhythmias, and ultimately sudden cardiac death. The pathophysiological processes contributing to electrical instability in the diabetic heart are summarized in Figure 3.

4. Sarcolemmal ATP-dependent potassium channels (K_{ATP}) link metabolic activity to excitability

K_{ATP} channels act as immediate metabolic sensors coupling electrical excitability to the cellular high-energy phosphate pool of cardiomyocytes. These channels occur in high density in ventricular cardiomyocytes and are hetero-octamers comprised of the pore-forming Kir6.2 (*KCNJ11*) subunits and the regulatory sulfonylurea receptor SUR2A (*ABCC9*).^{51–53} ATP is the main inhibitory channel ligand which binds to Kir6.2 subunits and keeps the channel closed under physiological conditions when intracellular ATP levels are high (~6–10 mM). O'Rourke and colleagues described repetitive and self-sustaining oscillations of $I_{K_{ATP}}$ which were closely associated with cyclical changes in the mitochondrial NADH/NAD⁺ redox state in cardiac myocytes subjected to metabolic stress.⁵⁴ However, glycolytically generated ATP seems to be more critical in regulating $I_{K_{ATP}}$ in mammalian ventricular myocytes than ATP generated by oxidative phosphorylation.⁵⁵ These observations were complemented by recent data showing that glyceraldehyde 3-phosphate dehydrogenase (GAPDH), a key glycolytic enzyme, serves as an accessory protein of the cardiac sarcolemmal K_{ATP} channel complex.^{56, 57} The physical association between Kir6.2 and GAPDH may have significant functional consequences on the K_{ATP} -channel, as this enzyme catalyzes the reaction of 1,3-bisphosphoglycerate production. 1,3-bisphosphoglycerate has been suggested to be an endogenous K_{ATP} -channel opener that has the ability to activate sarcolemmal K_{ATP} channels even in the presence of high levels of intracellular ATP.⁵⁸ Modulation of ATP binding by additional metabolic factors is also suggested by a two-fold higher IC_{50} for ATP-dependent inhibition of K_{ATP} channels in diabetic hearts compared to controls.⁵⁹ As a result, hypoxia-induced shortening of the AP due to activation of the K_{ATP} channels, occurs to a much greater extent in ventricular cells from diabetic rats.⁶⁰ Of note, this sudden increase in K_{ATP} conductance during ischemia is expected to produce a greater dispersion of refractoriness in the diabetic vs. non-diabetic heart, as AP prolongation due to down regulation of major repolarizing K^+ channels is characteristically seen in diabetic myocardium (see Section 3).

During hypoxia or ischemia, global and especially local ATP concentrations may fall below a critical level, leading to opening of the K_{ATP} channel. Interestingly, the ST-segment elevation often observed on the electrocardiogram in the ischemic heart is postulated to result from excess opening of ATP-sensitive potassium channels.⁶¹ The $I_{K_{ATP}}$ -induced shortening of the cardiac AP is cardioprotective by decreasing Ca^{2+} influx through $I_{Ca,L}$, thus preventing cellular Ca^{2+} overload and further decline of the ATP pool. In line with this finding, Kir6.2 (*KCNJ11*) knock-out mice developed lethal arrhythmias upon sympathetic stimulation.⁶² Contraction bands, pathognomonic of cytosolic calcium loading, were visible on autopsy throughout the ventricular myocardium of the Kir6.2-knockout, but not wild-type mice.⁶² These results suggest that Kir6.2 plays an essential role in the myocardial response to stress. However, excessive AP shortening, resulting from activation of $I_{K_{ATP}}$, can also increase the dispersion of repolarization between ischemic and non-ischemic regions of the myocardium and predispose to reentrant arrhythmias including VF. In contrast to the general cardioprotective action ascribed to $I_{K_{ATP}}$ opening, several animal studies also suggest a beneficial effect of $I_{K_{ATP}}$ -blockade by reducing the incidence of VT/VF in the setting of

ischemia reperfusion.^{63, 64} In the following sections we will review recent evidence regarding the upstream signaling events leading to opening of K_{ATP} channels.

5. Collapse of mitochondrial membrane potential activates IK_{ATP} thereby creating regions of non-excitability (“metabolic sinks”)

Mitochondria are the “cellular power plants”, as they supply most of the cell’s chemical energy in form of ATP. New evidence has emerged over the last decade, demonstrating that mitochondria are involved in a wide range of additional cellular processes, such as cell signaling, apoptosis, ischemic preconditioning, control of cellular differentiation and cell cycle regulation.⁶⁵ Important mediators that link metabolic activity to various cell signaling pathways are ROS. As a byproduct of activity in the electron transfer chain, it is estimated that up to 5% of the molecular oxygen consumed in mitochondria is converted to superoxide anions by complexes I and III.^{7, 66, 67} As ROS can be highly toxic to nucleic acids, proteins, lipids, and other cellular components, cardiomyocytes possess a highly efficient antioxidant defense system, consisting of superoxide dismutase, catalase and glutathione peroxidase. Ischemia/reperfusion or metabolic stress can produce local elevations of ROS in the myocardium⁶⁸ which, by a positive feedback mechanism described by Zorov et al., can trigger additional ROS-production (“ROS-induced ROS release”).⁶⁹ When the balance between ROS production and ROS scavenging is shifted towards ROS production, the accumulation of ROS (and particularly superoxide anion, O_2^-) increases the open probability of ion channels located in the inner mitochondrial membrane thereby depolarizing the mitochondrial membrane potential ($\Delta\Psi_m$).^{70–72} Importantly, local mitochondrial perturbations are transmitted to neighboring mitochondria with ROS implicated as key signal transducers.⁷³ As a result, a local collapse of the mitochondrial membrane potential can have an impact on the entire mitochondrial network.^{71, 74, 75} As variations in $\Delta\Psi_m$ and AP duration are highly correlated through opening of sarcolemmal K_{ATP} channels,⁷⁰ large regions of conduction block may be created in the setting of ischemia/reperfusion, producing a substrate for stable arrhythmias upon reperfusion. Therefore, this “metabolic sink” would be distinct from other forms of block of electrical propagation, including loss of cell-cell coupling by closure of gap junctions, regional uncoupling by anatomical barriers to conduction (e.g. scar tissue) or dynamic functional block due to heterogeneity of intrinsic electrophysiological restitution properties.⁷⁶

6. Role of non-ion channel genes linking metabolic activity to arrhythmias

Adenosine monophosphate-activated protein kinase (AMPK) is a serine/threonine kinase abundantly expressed in myocardial tissue.⁷⁷ It is comprised of a catalytic α -subunit and regulatory β - and γ -subunits assembled as a heterotrimer.^{78, 79} AMP-activated protein kinase functions as a metabolic sensor in cardiomyocytes. AMPK activation by an elevated ratio of AMP to ATP stimulates ATP-generating pathways and down regulates ATP-consuming pathways. Therefore, AMPK has been termed the “guardian of energy status” in the heart.^{79–81} Specific mutations in the $\gamma 2$ regulatory subunit of AMP-activated protein kinase (*PRKAG2*) have been shown to alter myocardial AMPK activity and cause a glycogen storage cardiomyopathy characterized by ventricular pre-excitation, atrial fibrillation, progressive conduction system disease and a variable degree of left ventricular hypertrophy.^{82–84} The structural abnormalities, including glycogen accumulation and left ventricular hypertrophy, suggest that electrical instability associated with *PRKAG2* mutations might arise secondary to extensive structural remodeling rather than as a primary result of the *PRKAG2* mutation. In this sense, it has been suggested that glycogen-filled cardiomyocytes contribute to the formation of muscular bundles between atria and ventricles that mediate ventricular preexcitation.⁸⁵ Alternatively, the high incidence of ventricular pre-excitation and atrioventricular conduction abnormalities observed across several metabolic gene defects may result from disruption of the developmental patterning of the atrioventricular ring.⁸⁶ The notion

that arrhythmias arise secondary to structural abnormalities has been challenged by the discovery of a family with a mutation in *PRKAG2*, in which affected family members displayed an arrhythmogenic phenotype starting in early childhood at a time when structural abnormalities and cardiac hypertrophy were absent.⁸⁶ Mechanistically, AMPK could directly modulate the activity of sarcolemmal ion channels, as demonstrated for the cardiac sodium channel.⁸⁷ Additionally, AMPK activity could affect electrophysiological processes via a wide variety intracellular signaling pathways. Most notably, AMPK can phosphorylate endothelial nitric oxide synthase⁸⁸ and p38 MAP kinase⁸¹, both of which have pleiotropic actions in the heart, including direct effects on ion channels. Even though the precise cellular mechanisms linking AMPK mutations to arrhythmias are still elusive, the finding that a mutation in a major regulator of cardiac energy metabolism causes arrhythmogenic activity supports the notion that alterations in cardiac bioenergetics are sufficient to cause arrhythmias independent of a precipitating event like ischemia/reperfusion.

In addition to AMPK mutations, several monogenic disorders affecting genes of lipid and glycogen metabolism present with arrhythmias. For instance, Bonnet et al. reported a series of 24 children in whom arrhythmias or conduction defects were the presenting symptom of various fatty acid oxidation disorders.⁸⁹ They suggested that the accumulation of arrhythmogenic intermediary metabolites of fatty acids, such as long-chain acylcarnitines, may be responsible for the arrhythmias.⁸⁹ However, these rare inherited disorders of fatty acid metabolism are commonly associated with cardiomyopathy, making it difficult to separate the arrhythmogenic predisposition from the underlying heart failure.

7. Altered metabolism in atria: cause and consequence of arrhythmias

Cha and colleagues have demonstrated that the propensity for sustained atrial fibrillation in dogs with pacing-induced heart failure robustly correlates with the cellular energetic state in the atria.⁹⁰ Failing atrial myocardium displays a profound bioenergetic deficit with reduced activities of the phosphotransfer enzymes creatine kinase (CK) and adenylate kinase (AK), and depletion of high-energy phosphates. Despite significant increases in the atrial effective refractory period (ERP) in failing hearts, an enhanced propensity to sustained AF was observed in HF. Intriguingly, AF duration correlated inversely with atrial ATP concentration, as well as AK and CK activity.⁹⁰ Likewise, atrial tissue samples from patients who developed atrial fibrillation post-operatively had significantly lower concentrations of glucose, beta-hydroxybutyrate, and acetate compared to patients who remained in sinus rhythm after surgery.⁹¹ These observations suggest that perturbations in bioenergetic homeostasis and myocardial substrate use contribute to electrical instability in atrial myocardium.

There is a growing body of evidence that metabolic activity and arrhythmias are interdependent: An impaired cellular energetic state not only predisposes to atrial arrhythmias, but atrial rhythm disturbances also influence metabolic activity. Transcriptomic studies in permanent human AF, for instance, identified a prominent dysregulation of transcripts with metabolic function in tissue samples from patients with AF compared to patients in sinus rhythm. Notably, there was a coordinated transcriptional down regulation of enzymes controlling fatty acid oxidation and concomitant up regulation of enzymes involved in glucose utilization.⁹² In a goat model of AF, phosphocreatine decreased by 60% in atrial myocytes after one week of AF, suggesting an enhanced demand for high-energy phosphates.⁹³ As phosphocreatine levels increased thereafter and returned to baseline levels after 16 weeks of AF,⁹³ compensatory mechanisms are assumed to be activated to restore the metabolic balance between energy demand and supply. The finding of a prominent up regulation of transcripts involved in metabolic processes in human⁹² and experimental models of AF⁹⁴ supports this notion. Consistent with these microarray expression data, a recent proteomic and metabolomic

study of human atrial AF samples showed that the majority of changes observed in fibrillating atria were related to energy metabolism.⁹¹

8. Correction of metabolic abnormalities: A novel antiarrhythmic strategy?

Data reviewed in this article has highlighted that altered metabolism can lead to arrhythmias via a variety of cellular pathways in myocardial cells. Life-threatening ventricular tachyarrhythmias are prevalent in virtually every cardiovascular condition associated with structural and/or functional abnormalities. Clinical trials such as CAST⁹⁵ and SWORD⁹⁶ revealed that, at least in post-infarction patients, ion channel-targeted antiarrhythmic therapy may lead to increased rather than reduced mortality. In AF, large clinical trials have failed to prove the superiority of a “rhythm control” over a “rate control strategy”,^{97, 98} possibly due to an increased mortality associated with antiarrhythmic therapy.⁹⁹ Thus, modulating only the electrical activity (i.e. ion channel function) has proven ineffective to prevent arrhythmias in the long-term. Instead, additional strategies are needed in order to correct the underlying pathophysiological processes and metabolic abnormalities that lead to maladaptive ion channel remodeling.

In this respect, several drugs that either increase metabolic efficiency by augmenting glucose metabolism and blocking muscle mitochondrial free fatty acid uptake (e.g. perhexiline, trimetazidine, ranolazine) and/or block late sodium currents (ranolazine) have shown benefits in small preliminary clinical trials.¹⁰⁰ Moreover, emerging evidence regarding the central role of mitochondria in maintaining electrical stability in the heart has led to the identification of several novel pharmacological targets. For instance, 4'-chlorodiazepam, a ligand of the mitochondrial benzodiazepine receptor, has proven effective in stabilizing the mitochondrial membrane potential primarily by blocking the mitochondrial inner membrane anion channel (IMAC) at the time of increased oxidative stress and protect against reperfusion arrhythmias and post-ischemic contractile impairment. Remarkably, unlike other pre-conditioning agents, 4'-chlorodiazepam, was effective when given as a single bolus upon reperfusion.¹⁰¹

Conclusion

It is apparent that there is an intimate relationship between energy metabolism and ion homeostasis. The varied ways in which altered metabolism can be arrhythmogenic provides valuable mechanistic insights and identifies potential molecular targets for pharmacological interventions to treat arrhythmias. Given the proarrhythmic risk associated with conventional, ion channel-targeted antiarrhythmic drug therapies, a new approach to arrhythmias is urgently needed. In this respect, correction of the cellular bioenergetic deficit associated with structural heart disease might represent a novel and promising antiarrhythmic strategy.

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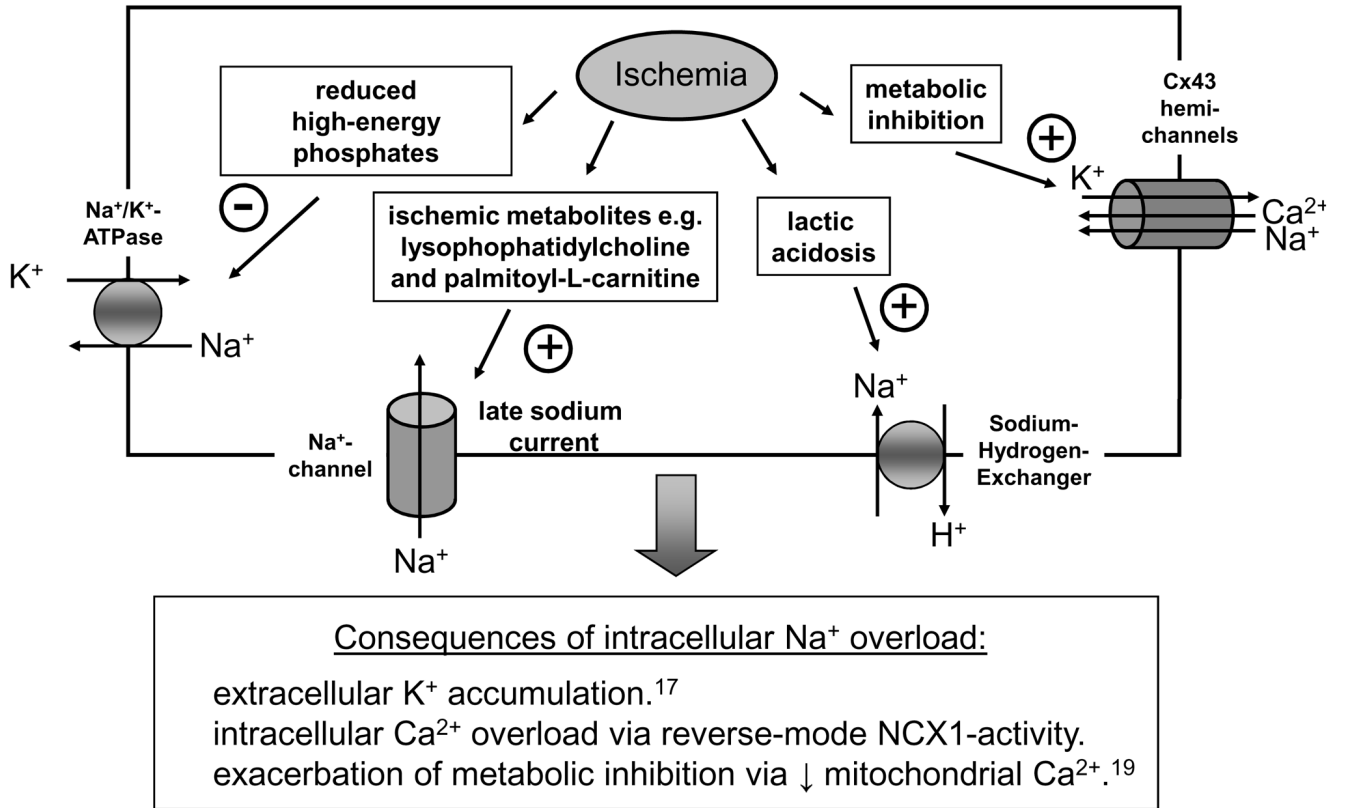


Figure 1. Pathophysiological processes associated with intracellular sodium overload during ischemia

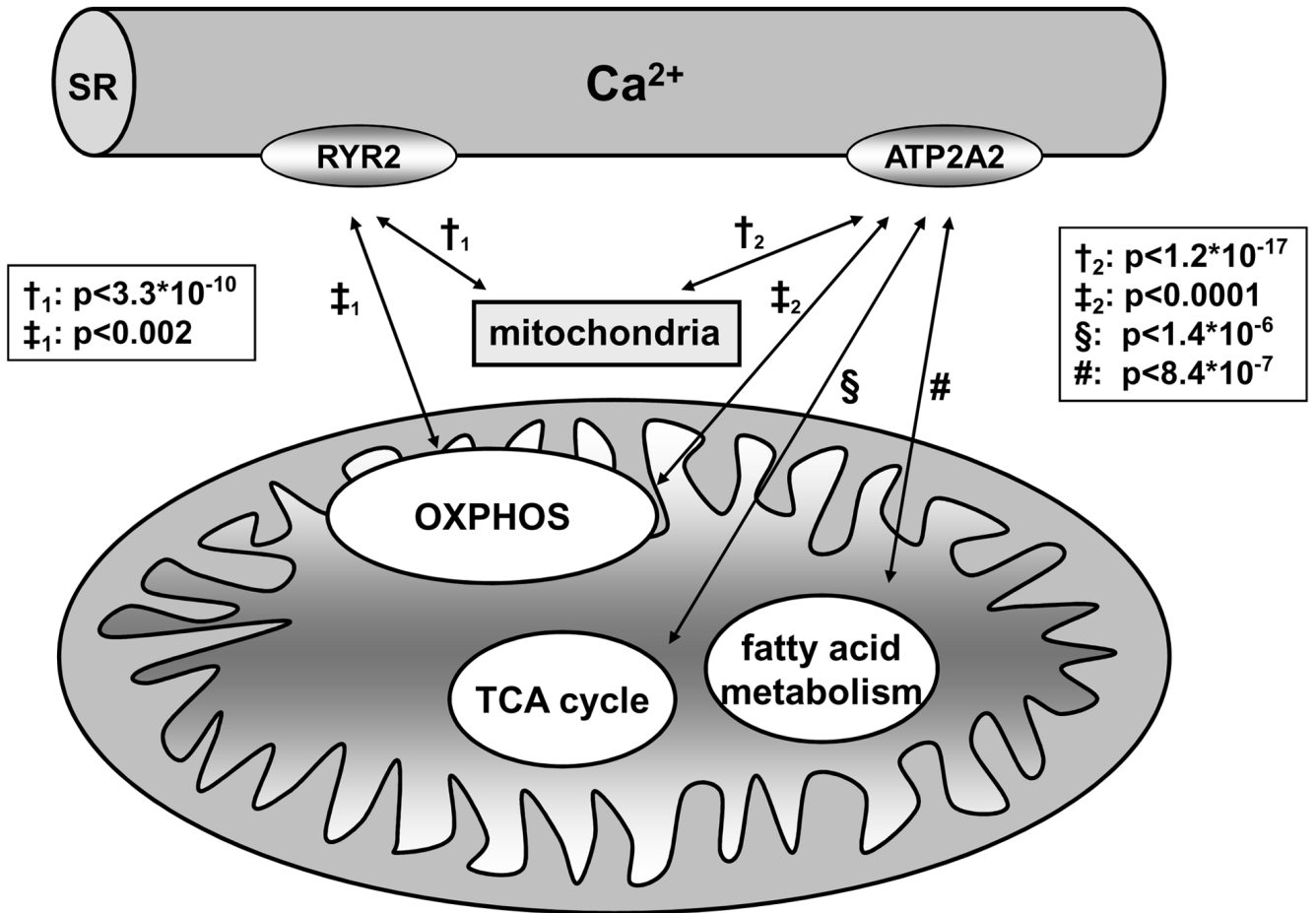


Figure 2. Transcriptional co-regulatory patterns for SERCA2 (ATP2A2) and RYR2 in mouse myocardium

Genes that were co-regulated with SERCA2 and RYR2 were identified by StarNet¹⁰² and grouped into Gene Ontology categories. Mitochondrial transcripts showed the most significant co-expression pattern with SERCA2 and RYR2. (Bonferroni corrected p-values for the correlation coefficient across 239 mouse microarrays are indicated). OXPHOS = oxidative phosphorylation.

Diabetes mellitus

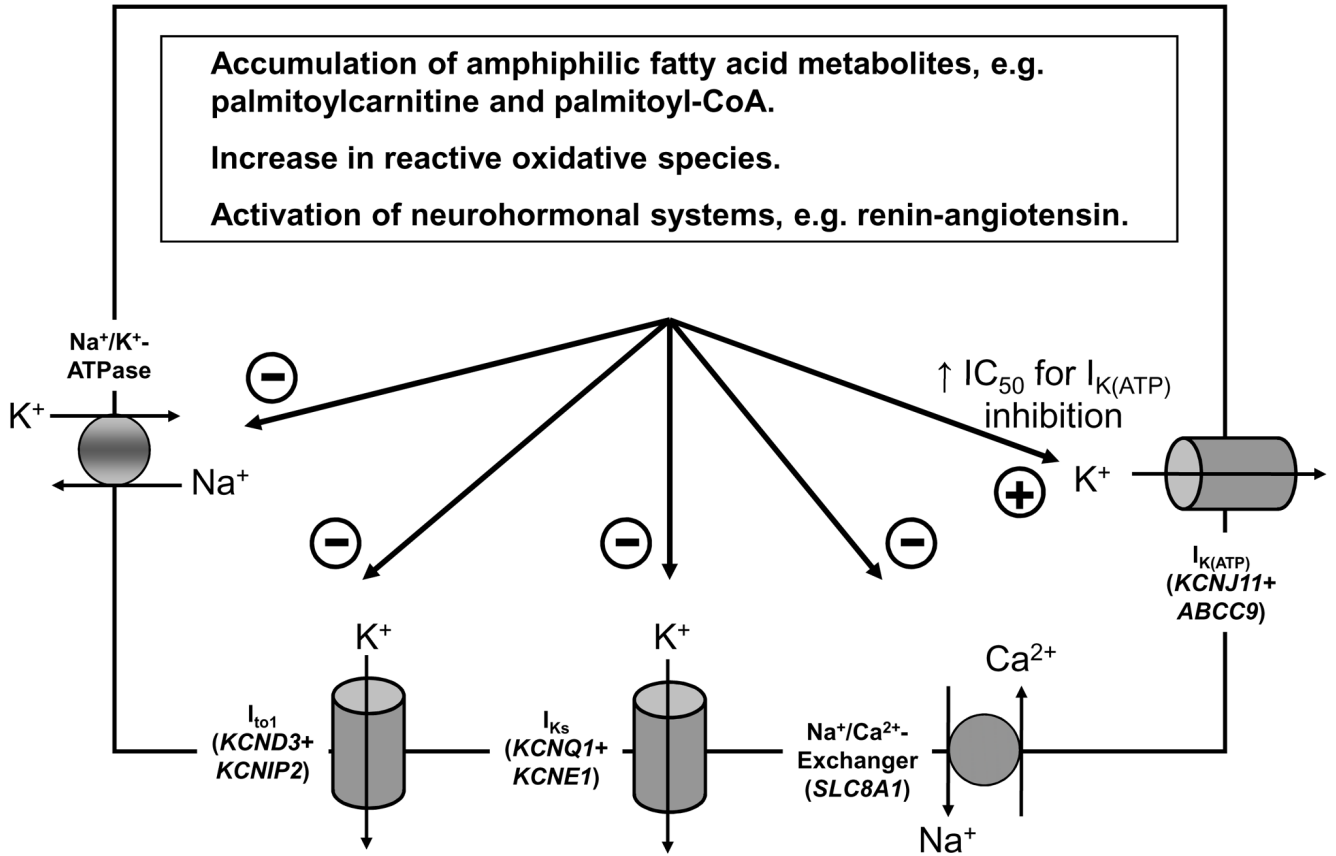


Figure 3. Pathophysiological processes associated with electrical instability in diabetic hearts