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Mitochondria and Arrhythmias

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Introduction

There is a clear relationship between cardiac mechanical dysfunction and arrhythmogenesis, and yet the mechanistic link is unknown. Mechanical dysfunction is accompanied by mitochondrial dysfunction, and in this review, we will discuss some of the ways mitochondrial dysfunction can lead to arrhythmogenesis, thereby providing a link between mechanical dysfunction and arrhythmias.

Mitochondria occupy around 30% of the mammalian myocardium by volume and are responsible for over 90% of cardiac ATP production[1]. In addition to energy production, mitochondria have been implicated as critical organelles involved in ion channel regulation, heat maintenance, apoptotic function, and regulation of reactive oxygen species (ROS)[2]. A growing field of research, coined mitochondrial medicine, is aimed at modifying mitochondrial function, in particular the generation of ROS, to alleviate disease burden attributed to mitochondrial stress[2;3]. The aim of this review is to discuss the role of mitochondrial dysfunction in arrhythmogenesis and to posit new antiarrhythmic therapies based on ameliorating mitochondrial dysfunction in cardiac disease. New information on mitochondrial regulation of sodium channels, potassium channels, and connexons will be discussed. Calcium handling and the mitochondrial permeability transition pore, both of which contribute to arrhythmogenesis and tissue injury following mitochondrial distress, have been reviewed elsewhere.

The mitochondria are organelles with two membranes that create two compartments: the intermembrane space and the mitochondrial matrix. Mitochondria function as key regulators of metabolism, utilizing oxygen and dietary substrates to generate ATP via oxidative phosphorylation (OXPHOS). During OXPHOS, electrons are collected from the oxidation

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of carbohydrates and fats to allow the production of reducing equivalents NADH and $FADH_2$. These reducing equivalents transfer their electrons to the electron transport chain (ETC) complexes along the inner mitochondrial membrane. As the electrons flow through the complexes of the ETC, H^+ is driven out of the mitochondrial matrix and sequestered into the intermembrane space. This creates a strongly negative mitochondrial membrane potential designated as $\Delta\psi_m$, that can be utilized to help target drugs to the mitochondria. Movement of H^+ down the proton-gradient across the inner membrane drives the final complex of the ETC, ATP synthase, which converts ADP to ATP.

As a by-product of OXPHOS, reactive oxygen species (ROS) are often produced. Incomplete reduction or a surplus of electrons in the ETC can result in partially reduced oxygen molecules, creating the reactive intermediate superoxide (O_2^-). The mitochondrial antioxidant protein, manganese superoxide dismutase (MnSOD), is responsible for converting O_2^- to H_2O_2, which can be further broken down by catalase. Mitochondrial ROS production is elevated beyond MnSOD's antioxidant capacity in a wide range of diseases, including diabetes, metabolic syndrome, cancer, and cardiomyopathy, and aging[3]. This mitochondrial stress results in the build-up of deleterious metabolites, such as NADH and ADP, and depletion of antioxidant defenses, such as glutathione[4;5]. Recent works in cardiology have implicated mitochondrial stress in arrhythmogenesis, allowing a potential new avenue for therapeutic approach.

Mitochondrial Regulation of Sodium Channels

Reduced cardiac voltage-gated sodium channel (SCN5A) current (I_{Na}) is known to contribute to arrhythmia[6]. Reduction of Na^+ channel conductance by 50%, as was demonstrated in a heterozygous SCN5A knockout mouse, has been shown to impair myocardial conduction and promote ventricular tachycardia (VT)[7]. Recent work by our group has demonstrated that increased cytosolic NADH, as a consequence of cardiomyopathy and mitochondria dysfunction, results in decreased I_{Na}. This work suggests a link between metabolism and I_{Na}[8]. The deleterious effect of NADH accumulation on I_{Na} can be ameliorated with NAD^+, the oxidized form of the nucleotide. NAD^+ supplementation acts via a membrane surface receptor to reverse the inducible VT in $SCN5A^{+/-}$ mice[9].

The link between increased NADH and decreased I_{Na} appears to be dependent on mitochondrial ROS production[9]. The negative effects of NADH accumulation can be blocked by treating cells with a number of ETC inhibitors (i.e. rotenone or malonate) or by scavenging ROS using the mitochondria-specific antioxidant, mitoTEMPO. Further, the decreased I_{Na} can be mimicked by generating mitochondrial ROS by inhibiting ETC complex III with antimycin A. These data suggest that NADH regulation of I_{Na} signals through a mitochondrial ROS-dependent manner and that mitochondrial ROS generation by complex III is sufficient to downregulate I_{Na}[9]. In myopathic animals, either NAD^+ or mitoTEMPO given systemically could ameliorate arrhythmic risk and reversed abnormal structural changes seen in mitochondria during cardiomyopathy[8;10]. These experiments promote the use of mitochondrial antioxidants and NAD^+ supplementation as potential therapeutic approaches to restoring Na^+ channel function and reducing arrhythmic risk.

Mitochondrial Regulation of Potassium Channels

Prolongation of the action potential because of opening of sarcolemmal ATP-regulated K^+ channels (sarcK_{ATP}) has been implicated in arrhythmogenesis following ischemia[11]. SarcK_{ATP} channels open during ATP depletion, hyperpolarizing the membrane, creating conduction block, and providing a direct link between energy availability and cardiomyocyte excitability[12]. Studies by Dr. O'Rourke and his colleagues have demonstrated that sarcK_{ATP} current corresponds with fluctuations in $\Delta\psi_m$[13]. Further, they have shown that opening of a small proportion of sarcK_{ATP} channels can create a current sink in the myocardium, capable of slowing or blocking electrical propagation in the myocardium. The connection between mitochondrial energy availability and decreased myocardial conductance as a result of sarcK_{ATP} opening has been coined 'metabolic sink'[14].

Clinical studies have confirmed that inhibition of sarcK_{ATP} opening is antiarrhythmic. Treatment with sulfonylurea drugs, which block sarcK_{ATP}, lowers the incidence of ventricular arrhythmia in heart failure[15]. Targeting mitochondrial stress upstream of sarcK_{ATP}, however, may provide a novel therapeutic opportunity.

A second group of ATP-regulated K^+ channels located on the inner membrane of the mitochondria (mitoK_{ATP}) has been implicated in arrhythmogenesis, but the data are less compelling. Activation of mitoK_{ATP} is believed to be critical in ischemic preconditioning and has been shown to regulate infarct size and arrhythmia. Opened mitoK_{ATP} channels decrease the $\Delta\psi_m$, which in turn lessens the driving force for mitochondrial Ca^{2+} influx and the initiation of apoptosis[16]. Researchers have demonstrated that blocking mitoK_{ATP} prevents the beneficial anti-arrhythmic effects seen with ischemic preconditioning. Opening mitoK_{ATP} channels pharmaceutically (using minoxidil, diazoxide, or BMS-191095) has had mixed results in preventing arrhythmia prior to ischemic insult, but no benefit when administered after ischemia[17;18].

Mitochondrial Regulation of Connexin43

Connexin43 (Cx43) is a gap junction protein that provides low-resistance current propagation through ventricular myocytes. Cx43 expression is known to be decreased following a range of cardiac insults. Activation of the tyrosine kinase c-Src, a known consequence of ROS overproduction, has been linked to Cx43 downregulation following MI[19]. Heart failure is associated with renin-angiotensin system (RAS) activation. In a mouse model of cardiac RAS activation, c-Src is activated and correlated with sudden arrhythmic death[20]. Prevention of mitochondrial ROS is sufficient to decrease spontaneous arrhythmia in these mice. Treatment with mitoTEMPO lowers mitochondrial superoxide production, inhibits mitochondrial structural abnormalities, prevents c-Src activation, restores Cx43 expression, increases conduction velocity, and reduces arrhythmia inducibility[10].

The pro-arrhythmic phenotype seen in the RAS activated mice can be replicated in a mouse model of mitochondrial stress. Transgenic mice with a heterozygous knock out of MnSOD demonstrate increased mitochondrial ROS, activated c-Src, decreased Cx43, slowed conduction velocity, and increased arrhythmic inducibility[21]. This work suggests that mitochondrial ROS alone is sufficient to increase the risk of arrhythmia, further implicating

mitochondrial ROS as a regulator of Cx43 expression and suggesting that inhibition of mitochondrial ROS may offer therapeutic benefit.

Conclusions

Mitochondrial dysfunction could be an important link between mechanical dysfunction and arrhythmic risk, and preventing mitochondrial ROS may prevent mitochondrial injury and reduce this deleterious signaling. The data above suggest that mitochondrial antioxidants may be antiarrhythmic by raising Na^+ channels and connexin43, by preventing mitochondrial ultrastuctural damage, and by preventing excessive KATP channel activation, addressing a variety of ion channel dysregulations occurring with cardiac disease. Moreover, this approach has less likelihood of proarrhythmic side effects than current ion channel blocking strategies.

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