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Review Article

Mitochondria and arrhythmias

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ABSTRACT

Mitochondria are essential to providing ATP, thereby satisfying the energy demand of the incessant electrical activity and contractile action of cardiac muscle. Emerging evidence indicates that mitochondrial dysfunction can adversely affect cardiac electrical functioning by impairing the intracellular ion homeostasis and membrane excitability through reduced ATP production and excessive reactive oxygen species (ROS) generation, resulting in increased propensity to cardiac arrhythmias. In this review, the molecular mechanisms linking mitochondrial dysfunction to cardiac arrhythmias are discussed with an emphasis on the impact of increased mitochondrial ROS on the cardiac ion channels and transporters that are critical to maintaining normal electromechanical functioning of the cardiomyocytes. The potential of using mitochondria-targeted antioxidants as a novel antiarrhythmia therapy is highlighted.

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Introduction

The normal functioning heart requires coordinated, rhythmic electrical activity and contractile action. At rest, the heart pumps about 280 l of blood throughout the human body per hour, and the energy demand to meet this unceasing action consumes nearly 10% of the total body O_2 uptake [1]. Over 90% of the cellular ATP consumed in the heart is produced by the mitochondria through oxidative phosphorylation (OXPHOS) [2]. As the predominant energy generator in the heart, mitochondria account for ~30% of the volume of cardiac cells, forming a network surrounding the sarcoplasmic reticulum (SR), myofilaments, and t-tubules [3]. It is estimated that one-third of the cardiac ATP generated by mitochondria is used for sarcolemmal and SR ion channels and transporters, which are required for the electrical activity of the cardiac cells [4]. Therefore, mitochondrial dysfunction readily disrupts the cardiac rhythm by depleting energy supply to these channels and transporters [5,6].

In addition to producing ATP, mitochondria also generate reactive oxygen species (ROS) as a by-product of OXPHOS. It is

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now widely accepted that in addition to their critical bioenergetic function, mitochondria function as signaling hubs in large part by regulating redox signaling in the cell [7,8]. Under physiological conditions, trace amount of ROS establish a network of mitochondria-driven signals that integrate metabolism with gene transcription and enzymatic activity [9,10]. Short-term increases in ROS signals trigger adaptive responses and facilitate preconditioning, increasing cellular and tissue resistance against insult [11,12]. On the other hand, persistently elevated ROS levels can trigger maladaptive responses and persistent abnormalities that compromise function at the molecular, cellular, and tissue levels [13–15]; in this regard, excessive production of ROS elicits pathologic changes by altering cellular function and increasing cell death [16]. Emerging evidence has shown that excessive mitochondrial ROS production can impair cardiac excitability by affecting the function of various channels and transporters through direct interaction such as posttranslational redox modification of cysteine (S-glutathionylation, sulfhydration, and S-nitrosation) or tyrosine (nitration) residues [17–19]. Excessive mitochondrial ROS can also modulate ion channel/transporter function indirectly via associated signaling molecules, such as ROS-sensitive kinases, including calcium–calmodulin-dependent protein kinase (CaMKII), cSrc, and protein kinase C (PKC), or via redox-sensitive transcription factors, such as NF-κB [20–22].

Mitochondria are also critically involved in the homeostatic regulation of cellular cations such as Ca^{2+}, Na^{+}, and K^{+}, disturbance of which can have important consequences for cardiac contractility, energetics, and electrical activity [23–25]. There is a complex interrelationship between sarcolemmal and mitochondrial cation regulation. Mitochondria can take up and extrude Ca^{2+}, for example, modulating cardiomyocyte function by serving as a dynamic buffer for sarcolemmal Ca^{2+} [26,27]. Changes in sarcolemmal cation concentration, on the other hand, can influence mitochondrial structure [28,29], energetics [30,31], and mitochondria-dependent cell death [32]. Much of the mitochondria–sarcolemma cation interdependence is mediated by the ion channels or transporters located on the inner membrane of mitochondria (see below).

Many central metabolic systems operate totally or partially within the mitochondria. These systems dynamically regulate cellular energetic status and sarcolemmal ATP-sensitive potassium ($sarcK_{ATP}$) currents through oscillating mitochondrial membrane potential ($\Delta\Psi_m$) in response to the changes in the supply of fuel substrates and O_2 [33–35]. In the presence of metabolic stress such as myocardial ischemia, depolarization of $\Delta\Psi_m$ diminishes mitochondrial ATP production, resulting in the opening of the $sarcK_{ATP}$ channels, which creates a "current sink" in the myocardium, capable of slowing or blocking cardiac electrical propagation, thereby fomenting arrhythmias (see below) [33,36].

After a brief review on the ionic basis of cardiac excitability, mitochondrial energetics/ROS production, and mitochondrial/sarcolemmal cation homeostasis, the role of mitochondrial dysfunction in influencing myocyte excitability and cardiac arrhythmogenesis is discussed, with an emphasis on the impact of mitochondrial ROS on sarcolemmal and sarcoplasmic channel/transporter functioning. In addition, the potential antiarrhythmic therapies targeting mitochondrial dysfunction in cardiac diseases are highlighted.

Ionic basis of cardiac excitability and contractile function

The normal contractile function of the mammalian heart depends on proper myocardial electrical activity, including the sequential activation of cells in specialized conducting systems, the normal propagation of electrical activity through the myocardium, and the generation of action potentials in individual cardiomyocytes [37,38]. The normal cardiac cycle begins with the action potential originating in the sinoatrial node, propagating through the atria to the atrioventricular node. The electrical activity then spreads through the bundle of His and Purkinje fibers to the cardiac apex, exciting the working ventricular myocardium [39]. The propagation of myocardial electrical activity depends on electrical coupling mediated by gap junctions, ensuring the coordination of the electromechanical functioning of the working myocardium [40]. Myocardial action potentials are generated by the sequential activation and inactivation of ion channels conducting depolarizing, Na^{+} and Ca^{2+}, and repolarizing, K^{+}, currents [37,38]. During the action potential, Ca^{2+} influx through voltage-gated Ca^{2+} channels triggers the release of Ca^{2+} ions into the cytosol from the SR via ryanodine receptor 2 (RyR2). Ca^{2+} binds to the protein troponin-C of the troponin–tropomyosin complex, leading to cardiomyocyte longitudinal shortening. The synchronous shortening of the ventricular myocytes results in the contraction of the heart and the systolic ejection of blood [41]. The subsequent diastolic relaxation of the myocytes depends on the repolarization of membrane potential and the removal of Ca^{2+} from the sarcomere [41]. Myocardial action potential repolarization is determined by multiple outward K^{+} currents through voltage-gated K^{+} and inwardly rectifying K^{+} channels, whereas removal of Ca^{2+} from the sarcomere depends on sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA), which retrieves cytosolic Ca^{2+} into the SR, as well as the Na^{+}/Ca^{2+} exchanger (NCX), an antiporter membrane protein extruding Ca^{2+} from the cell. Factors that interfere with the aforementioned channel functioning may impair cardiac excitability and lead to cardiac arrhythmias.

Mitochondrial energetics and ROS production

The mitochondria are organelles containing a double-membrane structure (inner and outer membranes) that creates separate compartments, the intermembrane space and the mitochondrial matrix. Mitochondria utilize glucose and fatty acids, the primary metabolic substrates for the myocardium, to generate ATP through OXPHOS. Glucose and fatty acids are sequentially oxidized to produce acetyl-CoA, the metabolic intermediate allowing the production of reducing equivalents of nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide ($FADH_2$) through the tricarboxylic acid (TCA) cycle. These reducing equivalents feed electrons to the electron-transport chain (ETC) along the mitochondrial inner membrane, where the electrons flow through the complexes (I, II, III, and IV) of the ETC and finally to molecular oxygen to produce H_2O. As electrons flow through the ETC, redox reaction occurs at complexes I, III, and IV, which drives protons (H^{+}) across the inner membrane, from the mitochondrial matrix into the intermembrane space, establishing the proton gradient and the strongly negative mitochondrial $\Delta\Psi_m$ (approx -180 to -240 mV). The energy stored in the $\Delta\Psi_m$ and proton gradient drives H^{+} flow through mitochondrial ATP synthase (complex V), the final complex of the ETC, back into the matrix, converting ADP to ATP (Fig. 1).

As an inevitable by-product of OXPHOS, ROS are produced as a result of incomplete reduction or a surplus of electrons in the ETC. The relationship of OXPHOS to ROS production is not entirely clear and is probably not always an inverse proportion [42], but it has been estimated that 0.1–1% of the electrons flowing through the ETC prematurely leak to O_2 at complex I, II, or III, causing the formation of superoxide ($O_2^{\bullet -}$), one of the major ROS in cardiac cells (Fig. 1) [43]. The rate of ROS production in mitochondrial matrix depends on the proton-motive force, the $NADH/NAD^{+}$ ratio, the reduced coenzyme Q10 ($CoQH_2$)/coenzyme Q10 (CoQ) ratio, and the local O_2 concentration. Under conditions of high