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Mitochondrial Adenine Nucleotide Transport and Cardioprotection

Samarjit Das and Charles Steenbergen

Department of Pathology, Johns Hopkins University, Baltimore, MD

Abstract

Mitochondria are highly metabolically active cell organelles that not only act as the powerhouse of the cell by supplying energy through ATP production, but also play a destructive role by initiating cell death pathways. Growing evidence recognizes that mitochondrial dysfunction is one of the major causes of cardiovascular disease. Under de-energized conditions, slowing of adenine nucleotide transport in and out of the mitochondria significantly attenuates myocardial ischemia-reperfusion injury. The purpose of this review is to elaborate on and update the mechanistic pathways which may explain how altered adenine nucleotide transport can influence cardiovascular function.

Keywords

Mitochondria; Adenine nucleotide transport; Cardioprotection

HISTORY OF MITOCHONDRIA

The first fossil evidence of life dates back nearly 3.5 billion years ago. The first evidence of eukaryotes arose around 1.5 billion years ago [1–3]. A popular theory to explain the evolution of eukaryotic cells, serial endosymbiosis, also provides an explanation for the origin of mitochondria [1–3]. Mitochondria are suggested to be direct descendants of α -Proteobacteria, a group of obligate intracellular parasites that includes *Rickettsia*, *Anaplasma*, and *Ehrlichia*, which lived as an endosymbiont [1, 3, 4]. It is not clear whether formation of the nucleus or other cellular compartments evolved before or after the endosymbiotic event of the host cells [4]. It is speculated that the mitochondrial membrane was derived from the endosymbiont, which also had a double-membrane [1, 5]. Hence, the bacterial periplasm would be equivalent to the mitochondrial inter-membranous space and the bacterial cytosol would be the mitochondrial matrix. The functional activities of mitochondria also resemble bacteria. For example, the inner membrane generates membrane potential ($\Delta\Psi$) using respiratory chain complexes, which provides the energy for ATP synthesis [6]. The evolution of mitochondria explains their status as semi-autonomous organelles in a cell, as they have their own DNA, mRNA, tRNA, and ribosomes [7, 8].

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Correspondence: Charles Steenbergen, M.D., Ph.D., Dept. of Pathology, Cardiac Division, Johns Hopkins University, Baltimore, MD 21205, USA, Tel: (410) 502-5982, Fax: (410) 502-5862, csteenb1@jhmi.edu.

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MITOCHONDRIA: A PRIME TARGET FOR CARDIOPROTECTION

In 1986, Murry et al. [9] opened a new area of research when they described a phenomenon that produces an energy sparing effect during a sustained ischemic insult of the heart, known as ischemic preconditioning. Later, this group and others [10, 11] recognized that ATP utilization of the preconditioned myocardium was much slower than non-preconditioned myocardium. Slower ATP utilization translated into less stimulation of anaerobic glycolysis, attenuation in the fall in intracellular pH, and minimization of the ionic alterations that are characteristic of ischemia. Although it is very unlikely that this ATP preservation effect directly confers the protective effect from ischemic injury, it is plausible that the mechanisms responsible for ATP preservation and for the protective effect during preconditioning are related [12]. As such, studying mitochondria may help to resolve the mysteries of the energy-sparing effect of ischemic preconditioning.

UNDERLYING MECHANISMS INVOLVING MITOCHONDRIA

Recent studies of both cardioprotection and various forms of cell death, necrosis, apoptosis and/or autophagy, have focused on the central role of mitochondria. Several important targets for cardioprotection were identified that involved mitochondria, such as the activation of the mitochondrial K_{ATP} channel (mito K_{ATP}) [13, 14] or the translocation of connexin 43 into the mitochondria [15]. Our own studies identify two very important signaling molecules in the process of cardioprotection involving mitochondria, Bcl-2 and glycogen synthase kinase (GSK) [16, 17]. We have achieved cardioprotection by both cardio-specific overexpression of Bcl-2 [16] and also inhibiting GSK by using catalytic inhibitors of GSK [17]. Both are associated with a common phenomenon, the alteration of mitochondrial adenine nucleotide transport.

Bcl-2 REGULATES ADENINE NUCLEOTIDE TRANSPORT

Bcl-2, an anti-apoptotic protein, was first discovered as a protein overexpressed in a B-cell lymphoma due to a chromosomal translocation [18]. Recent studies not only revealed the anti-apoptotic role of Bcl-2, but also identified a role in regulating mitochondrial metabolism and function [16, 19, 20]. In a mouse model with cardiac-specific overexpression of Bcl-2, Chen et al showed that Bcl-2 protects against ischemia-reperfusion injury and attenuates apoptosis [21]. In addition to Chen et al's observations, other studies provided new insights into the mechanism by which Bcl-2 mediates cardioprotection involving altered mitochondrial adenine nucleotide metabolism [16]. Hearts overexpressing Bcl-2 had a slower rate of decline in ATP during the first few minutes of ischemia than wild-type mice hearts [16]. The protective effect can be explained by a slower rate of consumption of glycolytically generated ATP. During early ischemia, there would be more ATP, less acidosis, and therefore less ionic alterations, and less activation of degradative enzymes. If lethal cell injury is related to the time interval after ATP reaches a critically low value, then slowing the rate of ATP depletion would be protective. The reduction in ischemic acidification [16] would be beneficial because there is less activation of the Na^+/H^+ exchanger; which means less of a rise in cytosolic Na^+ . This simultaneously alters Na^+/Ca^{2+} exchange, thus limiting Ca^{2+} influx into the cell [22]. It has been shown by multiple studies that during ischemia, limiting the rise in cytosolic Ca^{2+} reduces ischemic injury [22]. Inhibition of the mitochondrial F_1F_0 ATPase eliminates the effect of Bcl-2 overexpression on ATP degradation. The 50% reduction of ATP consumption by the mitochondria, which ultimately slows the rate of anaerobic glycolysis, resulted in less ischemic acidification [22–24]. To investigate the possible role of the F_1F_0 ATPase, isolated mitochondria were de-energized with an uncoupler, and the rate of mitochondrial ATP hydrolysis was found to be significantly slower in the mitochondria from Bcl-2 overexpressed hearts or from the normal

hearts where recombinant Bcl-2 was added to the mitochondria, than in mitochondria from wild-type hearts [16]. A possible explanation would be that Bcl-2 translocates to the mitochondria, binds to a transporter, and prevents ATP from entering the mitochondria. Imahashi et al [16] investigated the Bcl-2 binding target using an immunoprecipitation approach. These experiments demonstrated co-immunoprecipitation of Bcl-2 and the voltage dependent anion channel (VDAC) in the outer mitochondrial membrane. These data are consistent with the previous finding of Bcl-2 family member proteins regulating VDAC transport of cytochrome c [25]. Furthermore, it was found that during ischemia more Bcl-2 interacts with VDAC. Further studies suggested that de-phosphorylation of VDAC in response to GSK inhibition, enhances Bcl-2 binding to VDAC, slowing down ATP entry into the mitochondria [17].

GSK REGULATES ADENINE NUCLEOTIDE TRANSPORT

Our recent studies suggest that a possible molecular target for GSK in the mitochondria is VDAC in the outer mitochondrial membrane. One mechanism for regulating VDAC activity may be post-translational modifications such as phosphorylation and dephosphorylation [17]. GSK, first identified as a regulator of glycogen metabolism, is also an important regulator of cell function, cell cycle, survival pathways, and apoptosis [26, 27]. GSK-3 belongs to the serine/threonine kinase family of proteins, and there are two known mammalian isoforms, GSK-3 α (MW 51 kDa) and GSK-3 β (MW 47 kDa), which are 98% homologous and share similar substrate specificity [27]. These two isoforms show weak identity in the C terminal residue [28]. Due to the presence of a glycine-rich region in the N-terminus, upstream kinases, such as Akt, can phosphorylate GSK-3 β on serine 9 and GSK-3 α on serine 21 [29]. The activity of GSKs are regulated by phosphorylation. Under normal conditions, the GSKs are active but upon phosphorylation, they are inactivated [26, 27]. In the heart, different GSK-3 isoforms play distinct roles in the regulation of cardiomyocyte proliferation during development and in response to myocardial infarction, and in hypertrophy and heart failure [30–32]. There are several signaling pathways known to regulate GSK-3 β activity by phosphorylation on serine 9, including Akt, Protein kinase C, Protein kinase A and many others [22, 27]. Previously, it has been shown that ischemic preconditioning inactivates GSK-3 β by phosphorylation on the serine 9 site. This is mediated by the PI3-kinase pathway during ischemic preconditioning [33]. Pretreatment and treatment at reperfusion with GSK-3 catalytic inhibitors can mimic ischemic preconditioning [33–35]. Interest in GSK-3 β increased when it was found that its cardioprotective effect correlates with its inhibitory effect on the mitochondrial permeability transition pore (mPTP) [33]. To answer some unresolved questions in terms of molecular targets for GSK-3 β and how GSK can modulate mitochondria, our group took a proteomics approach [17]. We have found that pretreatment with two different GSK-3 inhibitors protected against ischemic injury in the isolated rat heart [17]. We isolated mitochondria from three different perfused rat heart groups (control hearts and hearts treated with two different GSK-3 inhibitors) and de-energized them with the uncoupler dinitrophenol [17]. We also added two different interventions that are more physiologically relevant, more closely mimicking ischemic injury. These other protocols involved treating the mitochondria with the cytochrome oxidase inhibitor, cyanide, as well as making the mitochondria anoxic by stimulating respiration with ADP inside the sealed oxygraph chamber and extending the duration of treatment to allow the mitochondria to become de-energized. Regardless of the protocol, we have found that ATP hydrolysis with GSK-3 inhibitor treatment is significantly slower than in the control mitochondria [17]. The cardioprotective interventions, Bcl-2 overexpression [16] and GSK-3 inhibition [17] similarly altered mitochondrial adenine nucleotide transport, which may be one of the key mechanisms responsible for the protective effects. Using proteomics and an ATP-AMP assay, we identified the downstream target of GSK-3, VDAC, and we also demonstrated that the phosphorylation of VDAC affects

mitochondrial function [17]. GSK-3 inhibitor treatment not only reduced the phosphorylation of VDAC, but also increased Bcl-2 binding to VDAC [17]. This suggests that the phosphorylation of VDAC plays an important role either directly or indirectly by binding with other proteins in the outer mitochondrial membrane. This phenomenon likely contributes to the slower rate of ATP hydrolysis.

CENTRAL ROLE OF VDAC

We have found two interventions that alter mitochondrial adenine nucleotide transport, Bcl-2 overexpression [16] and GSK-3 inhibition [17], that target VDAC and are associated with altered phosphorylation of VDAC. Altered VDAC function plays an important role in the energy-conserving effect as a downstream target of both of these interventions. There are three different VDAC isoforms present in mammalian myocytes [12, 37, 38], which are responsible for transport of molecules up to 5000 kDa across the outer mitochondrial membrane. Nucleotides like ATP and ADP can penetrate the outer mitochondrial membrane when VDAC is in an open state and are virtually impermeant when VDAC is closed [12]. Closure occurs in response to either a positive or negative potential. There is evidence of a small potential across the outer mitochondrial membrane, but whether this varies and thereby plays a role in regulating mitochondrial function is unclear [37]. The role of phosphorylation in the regulation of VDAC function is also controversial, and may depend on the metabolic status of the cell and mitochondria, as well as whether the mitochondria are energized or de-energized, which VDAC isoform is phosphorylated, and the specific phosphorylation site. More work needs to be done to resolve the effects of VDAC phosphorylation on mitochondrial function in general and on transport across the outer mitochondrial membrane more specifically. Although as the name suggests, VDAC transports anions in a voltage-dependent manner, transport of cations is relatively voltage independent, and may actually increase in the voltage-induced closed state [39]. NADH modulates VDAC by causing a steep voltage dependence of VDAC behavior [40]. There is also evidence that tubulin can regulate VDAC transport through reversible permeation block [41]. Induction of VDAC closure may be protective during ischemia, although it may also be detrimental depending on the circumstances. The impact of VDAC closure on apoptosis is controversial. Shimizu et al [42] have shown that the BH4 domain of antiapoptotic Bcl-2 family members closes VDAC and inhibits apoptosis. In contrast, Vander Heiden et al suggest that VDAC closure is proapoptotic by preventing metabolite exchange between the cytosol and mitochondrial matrix [43, 44]. It has also been suggested that proapoptotic Bcl-2 family members such as Bid can induce VDAC closure [45], leading to reduced metabolite exchange between cytosol and mitochondria and ultimately to mitochondrial dysfunction. These differences may relate to the different protocols used to induce apoptosis, and the conditions present during apoptosis can be very different from the conditions of ischemia, where the mitochondria are a consumer of ATP rather than a producer. Because of the important role of VDAC as a regulator of mitochondrial function, as well as a regulator of apoptosis and ischemic injury, it would be highly desirable to have specific VDAC inhibitors. Unfortunately, we do not currently have such compounds, although phosphorothioate oligonucleotides have been found to be able to induce VDAC closure [46]. An alternative approach has been to use genetic manipulation to ablate specific VDAC isoforms, singly or in combination. Genetic manipulation has revealed that ablation of mouse VDAC1 [47] and VDAC3 [48] results in viable mice, but deficiency of VDAC2 is embryologically lethal. The fact that VDAC2 is an essential component for viability makes it difficult to test the role of this isoform in myocardial ischemia-reperfusion injury.

There has been growing interest in the concept of protein-protein interactions playing a regulatory role in VDAC function. This can potentially explain the slower adenine nucleotide transport through the outer mitochondrial membrane under de-energized

conditions. Several studies from our own laboratory [16, 17] involving VDAC-Bcl-2 interaction and also a study showing interaction between BH4 oligopeptides of Bcl-2 and Bcl-x_L binding to VDAC [42], provide support for this concept. Which specific VDAC isoform complexes with Bcl-2 or Bcl-2 family members has not been definitively established, but studies with cells expressing N-terminal truncated VDAC1 suggest that Bcl-2 can bind to the N-terminus of VDAC1 [49]. There is evidence that the cytosolic protein tubulin can interact with and modulate VDAC [41]. Kottke et al. [50] found hexokinase (HK) I specifically bound to VDAC and showed alteration in Ca²⁺ transport through the outer mitochondrial membrane in brain. Further work has shown that the association between HK, VDAC, and Akt plays an important role in mitochondrial function and regulation of the mitochondrial permeability transition and apoptosis [51–53]. Mitochondrial binding of HK II has been suggested to protect cells from apoptosis by interfering with the binding of proapoptotic Bcl-2 family members [54]. In cardiomyocytes, HK II has also been shown to bind with VDAC after Akt mediated phosphorylation [52]. Sun et al. [53] found both HK I and II to bind with mitochondria, specifically to VDAC, which confers the protective effects. Studies using VDAC1 null cells suggest that VDAC1 is the primary binding site for hexokinase [55], and in VDAC1/3 null cells, there was no detectable binding of HK II to VDAC2 [56]. Nevertheless, in the VDAC1/3 null cells, displacement of HK II from the mitochondria using an HK II N-terminal peptide resulted in mPTP opening and cell death, suggesting that the binding of HK II to VDAC1 may not be its primary role in regulating the mPTP. Several cardioprotective interventions, including ischemic preconditioning, have been shown to be associated with hexokinase redistribution [57]. Disruption of HK II binding to mitochondria is reported to accelerate cell death during ischemia/reperfusion injury and to block ischemic preconditioning by mitochondrial membrane depolarization [58]. Other recent work suggests that HK II dissociation may lead indirectly to loss of cytochrome c from the intermembrane space, removing an important ROS scavenger [59]. It has been demonstrated that PKCε phosphorylates VDAC1 when activated [60]. The same study also found that VDAC1 phosphorylation results in a higher binding affinity towards PKCε [60], which can inhibit mPTP opening. All of these studies emphasize a potentially important role for VDAC regulation in mitochondrial function, although the genetic ablation studies suggest that VDAC is not an obligatory molecule for mPTP opening or for apoptosis [56, 60]. Other forms of post-translational modification, such as S-nitrosylation, may also have a regulatory role in VDAC function, and recent work suggests that VDAC1, VDAC2, and VDAC3 can be S-nitrosylated in the heart, either as a consequence of ischemic preconditioning or treatment with an S-nitrosylating agent [61]. The effects of S-nitrosylation on VDAC function remains to be established, but S-nitrosylation does inhibit the mitochondrial F₁F₀-ATPase [62], and would have a similar effect on mitochondrial ATP consumption during ischemia as slowing of VDAC transport. The effects of phosphorylation on VDAC function varies with the different isoforms of VDAC. We found when VDAC2 is constitutively phosphorylated, and when it is dephosphorylated, this is protective against ischemic injury and increases the binding affinity with Bcl-2, thus slowing down ATP hydrolysis [16, 17]. However, others found that phosphorylation of VDAC1 is protective and increases the binding affinity with PKCε [60]. Thus, phosphorylation has different effects depending on which VDAC isoform is being phosphorylated as shown in figure 1.

Although several groups have found evidence that phosphorylation of mitochondrial proteins including VDAC [17, 60, 63] plays an important role in cardioprotection, Clarke et al. [64] did not find mitochondrial protein phosphorylation to be involved in the protective effect of ischemic preconditioning. Ischemic preconditioning inhibits GSK-3 by phosphorylation, and therefore, one might expect that ischemic preconditioning and GSK-3 inhibitor treatment would share a common mechanism. However, in the two different studies [17,64], tissue collection and processing were very different. Clarke et al. [64]

generated highly purified mitochondrial fractions through a lengthy isolation process while Das et al. [17] used total heart homogenate, frozen rapidly to minimize the opportunity for dephosphorylation. It is possible that VDAC phosphorylation is labile, and this modification can be lost during processing. Alternatively, there could be multiple phosphorylation sites on VDAC1 and VDAC2, some of which increase transport and some of which inhibit transport, which would complicate the analysis.

VDAC AND THE MITOCHONDRIAL PERMEABILITY TRANSITION PORE (mPTP)

Calcium overload, heavy metal accumulation, and oxidative stress open a non-specific pore in the mitochondrial membrane known as the mitochondrial permeability transition pore (mPTP). This pore is permeable to molecules of less than 1.5 kDa. Irreversible or persistent opening of this pore is generally believed to be the terminal event in ischemia-reperfusion injury and results in cell death. There is considerable debate concerning the specific protein constituents, and whether the pore involves only the inner mitochondrial membrane or both inner and outer mitochondrial membranes. There are also theories that the mPTP can have variable composition [65].

A significant number of groups put VDAC as one of the primary components of the mPTP in the outer membrane [66–68]. However, genetic manipulation suggests that the mPTP exists in cells lacking each of the VDAC isoforms, questioning whether any of the VDAC isoforms are obligatory components of the mPTP. VDAC1 and VDAC3 knock-out mice do not offer any protection against ischemia-reperfusion injury [48], suggesting that these isoforms are not critical for mPTP opening. When embryonic fibroblasts were isolated from the double knock-out (VDAC1 and VDAC3) mice and VDAC2 was silenced with siRNA and the mPTP was induced by oxidative stress, the VDAC null cells were indistinguishable from wild type [48]. Cardiac myocytes may be different from embryonic fibroblasts, but these data suggest VDAC may not be an obligatory component of the mPTP. Other outer membrane proteins may also have a regulatory role in mPTP opening [69].

The adenine nucleotide translocator (ANT) is a relatively small protein present in the inner mitochondrial membrane. It transports nucleotides in their fully ionized state with a reversible exchange of ADP for ATP with a 1:1 stoichiometry [40]. ANT inhibitors affect mPTP opening in opposite ways; bongkrekic acid, an inhibitor of ANT, has been found to inhibit mPTP opening during Ca^{2+} overload in the matrix [70], whereas carboxyatractylide, another ANT inhibitor, sensitizes the mPTP to Ca^{2+} . The binding of these inhibitors causes conformational changes in ANT and modulates its function. Although ANT had originally been recognized as a core component of the mPTP [70], recently this has been disputed after demonstration that ANT (ANT1 and ANT2) double knock-out mice still exhibit cyclosporine A (CsA)-sensitive mPTP opening, with a higher Ca^{2+} threshold [71] and with no sensitivity to ANT inhibitors. However, considering that adenine nucleotide transport across the mitochondrial membrane is essential for aerobic ATP production, other compensatory systems must exist, such as another ANT isoform apart from ANT1 and ANT2, or another carrier mechanism. Recent studies have suggested that the mitochondrial phosphate carrier (PiC) may be a component of the mPTP, and may be able to function as a pore even in the absence of ANT [70].

Cyclophilin-D (CyP-D) is one of the key regulators of mPTP, and its binding partner, CsA, is a potent inhibitor of mPTP [72–75]. CyP-D is a very low molecular mass (18 kDa) protein abundantly present in the matrix of mitochondria. Similar to the GST-CyP-D pull down assay, the CyP-D affinity column demonstrated a direct interaction between CyP-D and ANT [70]. Furthermore, pretreatment of this column with CsA prevented the binding of

ANT. An alternative view is that instead of complete inhibition, CsA desensitizes the mPTP, thus delaying its opening. Mitochondria isolated from the CyP-D knock-out mice were found to be resistant to Ca^{2+} -induced mPTP opening and behaved no differently from wild-type mitochondrial if both were treated with CsA [74–75]. Thus CyP-D is an accepted regulator of the mPTP, but does not appear to be part of the pore itself.

OTHER FACTORS IN MITOCHONDRIAL ADENINE NUCLEOTIDE METABOLISM

Although inhibition of ATP transport into the mitochondria is one mechanism that can contribute to slowing of ATP degradation during ischemia following cardioprotective interventions, mitochondrial ATP consumption can also potentially be curtailed by inhibition of the mitochondrial F_1F_0 -ATPase. Several mechanisms have been proposed to account for inhibition of the F_1F_0 -ATPase. Rouslin and colleagues [76] demonstrated that there is an endogenous mitochondrial ATPase inhibitor protein, IF_1 , that binds to the ATPase under de-energized conditions at low matrix pH and inhibits its activity. Divergent views have been expressed regarding the physiological role of F_1F_0 -ATPase inhibition in conserving ATP during ischemia. There is evidence implicating a role for F_1F_0 -ATPase inhibition in the preservation of ATP during ischemic preconditioning [77–78]. On the other hand, several groups have shown that preconditioning can be independent of mitochondrial F_1F_0 -ATPase inhibition [79–80]. However, this inhibitor protein is much more active in slow heart rate species such as rabbits and pigs, and has lower activity in mouse and rat heart [81–82]. This inhibitor may account for the much slower rate of ATP depletion in slow heart rate species than high heart rate species during ischemia, but since ischemic preconditioning is equally effective in rats, rabbits, and pigs, it is unlikely that this inhibitor is solely responsible for the effect of ischemic preconditioning on ATP consumption. Even in slow heart rate species, a study of inhibitor binding suggests that there is no significant difference between preconditioned and non-preconditioned myocardium [80] suggesting that this is not the explanation of the energy sparing effect of ischemic preconditioning [80]. Even if IF_1 does not play a consistent role in ischemic preconditioning, overexpression of IF_1 in cell models has been shown to reduce cell death during metabolic inhibition [83–84]. An alternative mechanism that could explain ATPase inhibition under at least some cardioprotective interventions is S-nitrosylation of F_1F_0 -ATPase subunits [62]. Most likely there are multiple mechanisms that can be induced by cardioprotective interventions that inhibit the F_1F_0 -ATPase, suggesting that inhibiting this important consumer of ATP during ischemia is an important aspect of cardioprotection.

Under aerobic conditions, mitochondrial creatine kinase and creatine phosphate play an important role in adenine nucleotide transport across the outer mitochondrial membrane (see ref 85), but this is likely to be less important during ischemia since tissue creatine phosphate falls rapidly during the first minute of ischemia [86].

CONCLUSIONS

Cardioprotective interventions are associated with an energy-sparing effect during the period of ischemia. It has been questioned whether this directly and significantly contributes to the protective effect, but the full mechanisms involved have not been clearly delineated and therefore it is difficult to prove or disprove their importance in protection. One mechanism that contributes to the energy-sparing effect is inhibition of mitochondrial ATP hydrolysis, which involves slowing of influx of glycolytic ATP into the mitochondrial matrix. In addition to preserving ATP, this would also be expected to affect mitochondrial function, resulting in accelerated dissipation of the mitochondrial membrane potential ($\Delta\Psi$). The driving force for calcium uptake into the mitochondrial matrix is $\Delta\Psi$ and therefore reducing

$\Delta\Psi$ would be expected to attenuate the rise in matrix calcium which would otherwise occur during ischemia, and evidence that mitochondrial calcium uptake under conditions of metabolic inhibition correlates with $\Delta\Psi$ has been provided by Ruiz-Meana et al [87]. How this impacts on the fate of the myocytes under conditions of ischemia and reperfusion remains to be established, but the data suggests that the outer mitochondrial membrane, especially VDAC, plays an important role in cardioprotection by altering adenine nucleotide transport across the mitochondrial membrane under de-energized conditions.

Acknowledgments

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Highlights

- Role of Mitochondria in Myocardial Ischemia-Reperfusion Injury
- Mitochondrial Adenine Nucleotide Transport in Ischemia-Reperfusion Injury
- Role of Voltage Dependent Anion Channel (VDAC) in Mitochondrial ATP Transport
- Mitochondrial ATP Transport and Mitochondrial Permeability Transition Pore (mPTP)

Figure 1.
Proposed mechanisms by which VDAC plays a central role in altered mitochondrial adenine nucleotide transport, which ultimately contributes to cardioprotection.