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The L-type Ca\(^{2+}\) channel: A mediator of hypertrophic cardiomyopathy

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It is well established that both calcium and reactive oxygen species (ROS) play a major role in myocardial function and the development of cardiac pathology. The L-type Ca\(^{2+}\) channel (I\(_{Ca-L}\)) is the main route for calcium entry into cardiac myocytes. Mitochondria are the main source of cardiac ROS production. We previously demonstrated that activation of cardiac I\(_{Ca-L}\) is sufficient to regulate mitochondrial function.\(^1\) Activation of I\(_{Ca-L}\) results in increased intracellular calcium that leads to an increase in calcium uptake into the mitochondria, increased mitochondrial NADH and elevated superoxide production. Activation of I\(_{Ca-L}\) also increases mitochondrial membrane potential (\(\Psi_m\)).\(^1\) We also identified a feedback loop between elevated mitochondrial ROS production and sustained activation of the I\(_{Ca-L}\).\(^1,2\) This sequence of events leads to the development of cardiac hypertrophy that involves activation of calcium-dependent signaling pathways.\(^3\)

Both I\(_{Ca-L}\) and mitochondria associate with cytoskeletal proteins. While the cytoskeleton plays a role in regulating cell morphology, there is increasing evidence that cytoskeletal proteins also assist with communication of signals from the plasma membrane to intracellular organelles. Therefore we examined the role of the cytoskeleton in regulating mitochondrial function in response to alterations in I\(_{Ca-L}\) activity. We demonstrated that in addition to calcium, the cytoskeletal network plays an important role in regulating \(\Psi_m\) in response to alterations in I\(_{Ca-L}\) activity.\(^2\) This calcium-independent response was facilitated by a physical link between I\(_{Ca-L}\) and mitochondria via the cytoskeletal network. The auxiliary \(\beta_2\) subunit of I\(_{Ca-L}\) plays an important role in regulating channel activation and inactivation kinetics. During the course of activation and inactivation the \(\beta_2\) subunit of the channel undergoes conformational movement. Both the \(\beta_2\) subunit of the channel and mitochondria associate with F-actin. We demonstrated that I\(_{Ca-L}\) is able to regulate \(\Psi_m\) via the cytoskeletal network when conformational changes in the channel occur during activation and inactivation, involving transmission of movement from the \(\beta_2\) subunit of the channel to the mitochondria.\(^2\) This involves alterations in the open/closed state of the mitochondrial voltage-dependent anion channel (VDAC), which has previously been shown to play a role in regulation of \(\Psi_m\).\(^2,4\)

If the cytoskeleton plays a role in mediating the effect of I\(_{Ca-L}\) on mitochondrial function, it is reasonable to assume that disruption of the cytoskeleton will alter the response. Using a murine model of familial hypertrophic cardiomyopathy that is characterized by disrupted cytoskeletal architecture we examined regulation of mitochondrial function by I\(_{Ca-L}\).\(^5\) Cardiac myocytes isolated from mice with disease causing cardiac troponin I mutation Gly203Ser (cTnI-G203S), exhibited altered I\(_{Ca-L}\) kinetics, and a significantly greater increase in \(\Psi_m\) and mitochondrial oxygen consumption (measured as an increase in flavoprotein oxidation and formation of formazan from tetrazolium salt) in response to activation of the channel.\(^5\) Consistent with our original hypothesis, the alterations in \(\Psi_m\) were not due to alterations in intracellular calcium, because the responses occurred under calcium-free conditions. Further to this, diastolic intracellular...
calcium levels were similar in cTnI-G203S versus wt mice under basal conditions, and in response to activation of ICa-L. We demonstrated that the response involved F-actin and β-tubulin and that the hyperpolarisation of the $\Psi_m$ occurred due to increased block of mitochondrial VDAC by β-tubulin. This finding is supported by studies demonstrating that β-tubulin associates with and regulates the open/closed state of mitochondrial VDAC. Overall, our findings provide important mechanistic insight into the development of Gly203Ser hypertrophic cardiomyopathy. We find that impaired communication between ICa-L and the mitochondria via the cytoskeletal network is associated with development of a hypermetabolic state (Fig. 1). These findings are commensurate with the stiff myocardium and hypercontractile hearts observed on echocardiography in patients with the Gly203Ser mutation.

With new mechanistic insight the question remains – can we improve current hypertrophic cardiomyopathy therapy? Administration of ICa-L inhibitor diltiazem to patients with hypertrophic cardiomyopathy has been shown to reduce the hypertrophy in some patients but with varied responses. In our recent study, we demonstrated that exposure of cTnI-G203S myocytes to diltiazem significantly normalizes $\Psi_m$ in response to activation of ICa-L. These data suggest that ICa-L antagonists may be effective in reducing the cardiomyopathy by altering mitochondrial function. It is important to note that similar alterations in ICa-L kinetics and mitochondrial metabolic activity were recorded in cardiac myocytes isolated from cTnI-G203S mice that not yet developed the cardiomyopathy. That is, myocytes isolated from pre-cardiomyopathic hearts also exhibited altered ICa-L kinetics, and a significantly greater increase in $\Psi_m$ and metabolic activity in response to activation of ICa-L. This finding is of major significance because it indicates that alterations in ICa-L and mitochondrial function in mice exhibiting the Gly203Ser mutation precede development of the disease. From a clinical perspective, these data suggest that early intervention with ICa-L antagonists as a means of normalizing cardiac metabolic activity in patients carrying the gene mutation prior to manifestation of the phenotype, may prevent development of the cardiomyopathy. The advent of new technologies for screening of “at-risk” patients with identified gene mutations may facilitate improved intervention and prevention of hypertrophic cardiomyopathy.

**Abbreviations**

AHNAK subsarcolemmal stabilizing protein  
cTnC cardiac troponin C  
cTnI cardiac troponin I  
cTnT cardiac troponin T  
ICa-L L-type Ca$^{2+}$ channel  
Mito mitochondria  
ROS reactive oxygen species  
VDAC voltage-dependent anion channel  
$\Psi_m$ mitochondrial membrane potential

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**References**


