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Mitochondrial Buffering of Calcium in the Heart

Potential Mechanism for Linking Cyclic Energetic Cost With Energy Supply?

Patrick G. Sullivan, C. William Balke, Karyn A. Esser

The kinetics of mitochondrial Ca^{2+} cycling and its precise role in controlling local Ca^{2+} fluxes in intact cardiac myocytes has not been fully elucidated. In the case of cardiac excitation–contraction (E-C) coupling in normal cardiac atrial cells, it has been established that cytosolic Ca^{2+} ($[Ca^{2+}]_c$) increases peripherally within the cell and propagates to the center.[1] What is less clear has been the understanding of the time scale dynamics of the Ca^{2+} fluxes within the mitochondria. To began to address whether beat-to-beat changes in $[Ca^{2+}]_c$ alter mitochondrial Ca^{2+} loading, Maack and colleagues[2] use a novel technique to monitor, simultaneously, Ca^{2+} concentrations in the cytoplasm and mitochondrial matrix. Additionally, the authors' probe the effect that mitochondrial Ca^{2+} efflux, due to elevated Na^+, could have on mitochondrial Ca^{2+} buffering and bioenergetics. It is well recognized that the energetic cost of mechanical/contractile work plus ion handling associated with E-C coupling is very high and is supported by the large mitochondrial volume fraction of the cardiac myocyte. The link between regulation of ATP production and intracellular calcium fluxes has been suggested by studies that have demonstrated that the transport of Ca^{2+} into the mitochondrial matrix can activate several enzymes of the TCA cycle.

It is well-known that mitochondria sequester Ca^{2+} ($[Ca^{2+}]_m$) under conditions that increase $[Ca^{2+}]_c$ concentrations in many different cell types.[3–5] Changes in $[Ca^{2+}]_m$ can have effects on energy production rates, amplitude, and temporal profiles of $[Ca^{2+}]_c$ as well as its well described role in the initiation of cell death pathways.[6,7] However, in cardiomyocytes, it is still debated whether or not mitochondrial Ca^{2+} uptake mechanisms can respond rapidly enough to accommodate beat-to-beat oscillations in $[Ca^{2+}]_c$. The two mechanisms described for mitochondrial Ca^{2+} uptake in cardiomyocytes are the electrogenic mitochondrial Ca^{2+} uniporter (mCU) and a mechanism termed "rapid mode of uptake" (RAM).[8] mCU Ca^{2+} uptake is driven in a Nerstian fashion that is dependent on the mitochondrial membrane potential ($\Delta\Psi$ component) and extra-mitochondrial Ca^{2+} concentrations.[9,10] Although the RAM uptake mechanism has been proposed to be at least 300 times faster than uptake via the mCU, it can only play a limited role during cardiac $[Ca^{2+}]_c$ oscillations because of it's slow recovery (>60 sec) after activation.

The mCU is a highly selective ion channel and has an exceptionally high affinity for Ca^{2+} ($K_d < 2$ nM) that allows it to be highly selective for Ca^{2+} even under conditions where $[Ca^{2+}]_c$ are extremely low.[11] The mCU is also inwardly rectifying which allows changes in $\Delta\Psi$ to modulate mitochondrial Ca^{2+} uptake irrespective of $[Ca^{2+}]_c$ such that depolarization results in a reduction in mitochondrial Ca^{2+} uptake. These properties also predict that mitochondrial Ca^{2+} uptake will have a biphasic temporal pattern because of the electrogenic nature of the mCU with Ca^{2+} uptake being countered by proton extrusion which reduces the $\Delta\Psi$ component of the mitochondrial membrane potential. Two Ca^{2+} efflux mechanisms exist in mitochondria of which one is Na^+-dependent and the other is Na^+- independent. In heart mitochondria, it is currently thought that the Na^+/Ca^{2+} is the primary efflux mechanism.[12]

Presently, two different theories have been put forth to explain how mitochondria can decode rapid oscillations in $[Ca^{2+}]_c$. In 1990, Crompton put forth the first scenario, which depends on a slow uptake of Ca^{2+} that is coupled to an even slower efflux of Ca^{2+}, allowing fast $[Ca^{2+}]_c$ oscillations to be integrated solely by Ca^{2+} transport machinery in the mitochondrial inner membrane.[13] This model allows for increases in either the amplitude or frequency of $[Ca^{2+}]_c$ to result in a cumulative increase in $[Ca^{2+}]_m$ until a steady-state is reached in which Ca^{2+} uptake equals Ca^{2+} efflux during a single cycle.[13] This scenario allows for small beat-to-beat changes in $[Ca^{2+}]_m$ which reduce the energetic costs of Ca^{2+} transport in mitochondria.

In contrast, the second theory hypothesizes that changes in $[Ca^{2+}]_c$ are translated directly into changes in $[Ca^{2+}]_m$, which requires the existence of both a rapid Ca^{2+} uptake and efflux mechanism to be active in mitochondria. It also requires that mitochondrial Ca^{2+} uptake be sufficient to overcome endogenous buffering of $[Ca^{2+}]_c$ for changes in mitochondrial matrix Ca^{2+} to occur during each contraction. It also predicts that $[Ca^{2+}]_c$ transients during E-C coupling would be effectively buffered by mitochondrial Ca^{2+} uptake. This logic in turn requires that SR Ca^{2+} uptake and release dynamics would have to be sufficiently large enough to compensate for this increased buffering by mitochondria.[14]

The current report by Maack and colleagues[2] critically examines the role of mitochondrial Ca^{2+} buffering in cardiac

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myocytes during contractions using a novel method to monitor $[Ca^{2+}]_c$ and $[Ca^{2+}]_m$ in the same cell. Their findings demonstrate: (1) that mitochondria take up Ca^{2+} rapidly and buffer $[Ca^{2+}]_c$ during E-C coupling, (2) the kinetics of the mitochondrial Ca^{2+} fluxes support the concept of "mitochondrial microdomains", and (3) elevation of Na^+ in the cytosol reduces mitochondrial Ca^{2+} flux which impairs energy production by altering the NADH/NAD^+ redox potential.

The finding that mitochondria rapidly sequester Ca^{2+} during E-C coupling directly supports the theory that fluxes in $[Ca^{2+}]_c$ directly encode changes in $[Ca^{2+}]_m$. As the authors point out, this type of rapid signaling could act to couple energy production in the mitochondria with increases in ATP demand. This concept is very intriguing and suggests a model in which the calcium buffering of the mitochondria provides fine rheostat control to allow for the matching of energy/ATP production with demand. As a general rule, the intracellular concentration of ATP within a cardiac myocyte does not decrease significantly even under the highest energetic demands. Thus, the cell must have a mechanism in place to rapidly respond to significant increases in ATP consumption in a manner that does not lead to increased ATP supply. The authors also demonstrate that it is likely that the microdomain of the mitochondria and its proximity to the SR junction provide the necessary local calcium concentrations required to induce the rapid influx. The concept of mitochondrial microdomains within cells is becoming common and well accepted,[15] but the demonstration in this article[2] of a mitochondrial microdomain is the first to illustrate the critical local information flow in cardiac myocyte mitochondria.

Finally, the authors assess the role of the mitochondrial Na^+/Ca^{2+} exchanger on $[Ca^{2+}]_c$, $[Ca^{2+}]_m$, and mitochondrial bioenergetics. Surprisingly, increasing the concentration of Na^+ increased $[Ca^{2+}]_c$ and accelerated the decay of $[Ca^{2+}]_m$. This could be interpreted as an indication that the limiting factor for mitochondrial Ca^{2+} efflux is Na^+ movement. This is interesting because it provides a model through which impaired sodium homeostasis in the cardiac myocyte seen in different pathologies could lead to mismatched signaling response of the cardiac myocyte to the calcium signal from E-C coupling. However, these interpretations need to be made with some caution, as the levels of Na^+ used in this work were quite high and could be triggering an effect not detected outside the normal physiological range. Nonetheless, this work has broad implications for cardiac disease, pharmacological treatment, and the cell biology through which the energetic cost of work is finely tuned to ATP supply mechanisms.

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Disclosures

None.

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