Mitochondrial Energetic Homeostasis and Parallel Activation

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***Short Abstract* —** Both skeletal muscle and cardiac muscle have the special ability to maintain energetic homeostasis in response to drastic elevations in energy expenditure. To meet this tremendous demand of ATP, mitochondrial oxidative phosphorylation has to increase in coordination. A metabolic network requires coordinated changes in fluxes, leading to the `in parallel activation' hypothesis. We propose a simple hypothesis that Ca^{2+} modulates mitochondrial energetic metabolism. We show that a mathematical model incorporating this hypothesis matches experimental data.

***Keywords* — mitochondria, oxidative phosphorylation, calcium**

I. Purpose

MITOCHONDRIAL oxidative phosphorylation supplies the vast majority of energy in metazoans. In humans, the change in ADP and Pi concentrations between exercising and resting muscle is small even though the ATP demand increases by almost an order of magnitude[1]. The canonical feedback regulation of energetic homeostasis by ADP and Pi is supported by some studies, but may not induce enough ATP production due to the minor changes in concentrations of metabolites. The `in parallel activation' hypothesis due to Korzeniewski[2] suggests using activation factors for metabolic enzymes to achieve the required coordinated changes in fluxes via simultaneous activation. The exact mechanisms for such an activation remain unclear. Metabolic enzymes are associated with regulation at different levels, e.g. phosphorylation, but perhaps calcium is the most important and ubiquitous factor impacting metabolism. Ca^{2+} not only is needed for muscle contraction, but also directly regulates various key enzymes in mitochondria. Recently, Glancy et al. evaluated the effect of Ca^{2+} on mitochondrial respiration in situ[3]. Their study provided new evidence that inter-mitochondrial Ca^{2+} alone can stimulate the entire energetic pathway simultaneously with similar magnitudes. Therefore, mechanisms may exist to coordinately induce the activities of those enzymes in vivo, as seen, for example, in [4-6].

II. Methods

This hypothesis was incorporated into a published mathematical model of mitochondrial metabolism[7]. We assumed that the metabolic enzymes have two forms: a basal form or an active form in the absence or presence of Ca^{2+}. Ca^{2+} can activate reactions by inducing the conversion from the basal form to active form. This new model was validated to fit the steady-state Ca^{2+} -dependent responses of muscle mitochondrial respiration in State 4 or State 3. Model simulations were compared with experimental results from the creatine kinase clamp protocol.

III. Results

Model simulations match experimental data[3]. The metabolic responses in State 4 and State 3 are remarkably different. In the absence of Ca^{2+}, oxygen consumption (JO_2) in State 3 was almost three times that in State 4. With added Ca^{2+}, oxygen consumption in State 4 was almost constant. In State 3, it increased and reached a plateau. In the absence of Ca^{2+}, the fraction of NADH in total NAD+NADH (%NADH) was ~100% higher in State 4 than in State 3. With the addition of Ca^{2+}, %NADH in both states increased with similar patterns. The membrane potential in State 4 was much higher than in State 3 in the absence of Ca^{2+}. Compared with its effect on JO_2 and %NADH, Ca^{2+} had negligible effect on membrane potential. JO_2 is almost linearly related to ΔG_{ATPe}, and the slope in the presence of Ca^{2+} is greater than in its absence. With the increase of ADP, the increase of JO_2 in the presence of Ca^{2+} was much larger than its increase in the absence of Ca^{2+}. The Eadie-Hofstee plots of JO_2 and ADP exhibit a near linear relationship. JO_2 is almost linearly related with membrane potential and the slope in the presence of Ca^{2+} is larger than in its absence.

IV. Conclusions

In parallel activation modulated by calcium concentrations is a viable mechanism for the observed ability of muscle mitochondria to maintain almost unchanged concentrations of metabolites under large changes in energy demand.

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