In Vivo Regulation of Mitochondrial Respiration in Human Skeletal Muscle: Potential Role of Changes in Oxidative Capacity With Work

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Purpose
The purpose of this study was to examine how current models of respiratory control in skeletal muscle would be affected by changes in oxidative capacity (maximal rate of ATP production) with changes in workload.

Introduction
A number of studies report that the signal transduction system for mitochondrial oxidative phosphorylation in skeletal muscle is more complicated in vivo than has been determined for isolated mitochondria, which, according to most reports, exhibit a Michaelis-Menten type dependence of oxygen consumption with [ADP] (Km of around 30μM) [review see 1]. While some reports indicate that the same relationship exists in certain types of skeletal muscle in vivo [2], others have shown that the apparent kinetic order of this relationship is at least second order [3], has a much higher Km [4], or is more complicated than a simple negative feedback system [5]. The two most prominent models of respiratory control are based on either a thermodynamic (VO2 as a linear function of cytoplasmic [ADP]) relationship or a kinetic (VO2 as a hyperbolic function of ADP) relationship. However, given the covariance of the constituents of these models it has been shown, at constant pH, that the models are indistinguishable [6]. Both models assume that "oxidative capacity or Vmax" is a static property of the system. This requires that the catalytic rate, apparent concentration, and substrate affinity for rate limiting enzyme(s) must remain constant during work. However, numerous studies have shown that energy metabolism is augmented during exercise by enzyme activation, temperature, hormones, blood flow and other effectors. In this study we have added a new term to existing models of respiratory control that allows oxidative capacity or Vmax to increase with increasing metabolic strain and evaluated the impact this may have on these models.

Methods
Existing models of respiratory control were modified to include a simple linear term for increasing oxidative capacity with increases in cytosolic [ADP] or decreasing ΔG'. Other functions may prove more realistic. The models then become:

\[ \text{VO}_2 = \frac{m(\Delta G')^2 + g_{\text{initial}}(\Delta G') + \text{VO}_{2\text{initial}}}{1 + K_a/\text{[ADP]}}, \]

where \( m \) is equal to the slope of the linear change in the mitochondrial conductance coefficient for the thermodynamic model and for the slope of the change in \( \text{V}_{\text{max}} \) for the kinetic model. \( g_{\text{initial}} \) is the mitochondrial conductance. These equations were then fitted to data where subjects were subjected to voluntary exercise of the tibialis anterior over a range of workloads supportable by aerobic metabolism using a custom designed ergometer [7]. 

Results
Figure 1 shows the PCr resynthesis rate as a function of last minute (A) [ADP] and (B) ΔG' relative to each individuals minimum value measured during exercise for the lowest metabolic strain (n=7 individuals). Minimum value averages were 63.7±32.7, 17.1±2.7, and -60.6±7.0 for \( R_s \), [ADP], and \( \Delta G' \), respectively. Dotted lines are fits using equations 1 and 2. Solid lines are standard hyperbolic and sigmoidal fits.

Discussion
By increasing the \( V_{\text{max}} \) as a function of workload, the conventional kinetic model could be fit to these data with reasonable affinity values for [ADP] based on in vitro values. In addition, the inclusion of the metabolic activation in the thermodynamic model was also feasible and consistent with the data. With the nature of these models (and in vivo SNR) neither were unique in describing the data collected in this study and thus provided little insight into mechanisms. However, the inclusion of alterations in metabolic capacity may provide a more realistic picture of this processes, based on the known metabolic activation associated with exercise. Incorporation of this factor into existing models may help reconcile in vivo and in vitro observations. Further studies will be required to determine the exact dependence of oxidative capacity on workload and better definition of the mechanisms involved in energy metabolism regulation.

References