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Control of respiration in skeletal muscle at rest

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Summary. The suggestion is made that, under resting conditions in situ, muscle cell respiration is dependent on the way O_2 and substrates are distributed to the cells by the microcirculation. (Delivery is measured as arterial-blood concentration multiplied by flow to the organ.) Microscale heterogeneity of this distribution, which is more marked but less stable than the more easily demonstrated larger-scale heterogeneity (0.1 to 0.5-g sampling grain), might indeed ration O_2 and substrates in a large population of the cells of a resting organ at any given moment, and microscale heterogeneity of distribution may thus take part in the normal control of cell respiration.
Key words. Skeletal muscle; cell respiration; maintenance metabolic rate; microcirculation; functional heterogeneity.

Introduction

I wish to draw attention to a *physiological* mechanism involving hypoxia in resting muscle. Limited transfer of oxygen or, more generally, limited transfer of substrates and products of oxidative metabolism between muscle cells and arterial blood perfusing the organ can be considered to be an integral component of respiratory control, and it is perhaps that component which allows muscle tissue maintenance at a low energy cost in the animal at rest. Any attempt to consider such an unorthodox viewpoint on respiratory control will meet with two major obstacles. First, the word hypoxia carries with it the idea that, somewhere, a *less-than-normal* amount of oxygen is available; second, feed-back matching of organ blood flow to organ metabolism is usually considered to occur at all aerobic metabolic rates, and this seems to imply a feed-back matching of capillary blood flow to cell metabolism at rest as well as in other aerobic steady-states.

Microscale heterogeneities in muscle

Using intravital microscopy and blood microsampling techniques, Duling and collaborators[4,6] have accumulated and confirmed direct evidence that feed-back matching of capillary O_2 availability to cell metabolism may not occur in skeletal muscle at rest. They observe a very significant heterogeneity of hemoglobin distribution to (and within) capillaries, and an equally marked microscale heterogeneity of blood flow distribution. The consequent heterogeneity of distribution of O_2 and substrate delivery to cells could limit the oxidative metabolism of a large population of cells in the organ at any given moment. The overall consequence would be a limitation of respiration in the muscle as a whole, despite non-limiting rates of delivery of O_2 and substrates to the organ. It has also been observed that constriction of the transverse arterioles leaving the muscle to enter the connective tissue may lead to a reduction of the local hematocrit (through accelerated movement of erythrocytes with respect to plasma) and the consequent diversion of red cells out of the muscle[14]. This particular kind of heterogeneity, however, does not seem to be the main cause of functional red-cell shunting in resting muscle.

Muscle oxygen consumption as a function of O_2 delivery

From the earliest to the most recent studies of the rate of muscle oxygen uptake ($\dot{M}_{O_2}$) as a function of the rate of oxygen transport to the organ ($\dot{T}_{O_2}$, which is the product of perfusate O_2 concentration and flow rate), two types of relationship have been observed. Some muscle preparations show *'O_2 conformity'*, that is, they *monotonously decrease* their $\dot{M}_{O_2}$ as $\dot{T}_{O_2}$ is decreased from a high value, by reducing either flow[7] or O_2 concentration[10]. Other preparations show *'O_2 regulation'*, that is, as $\dot{T}_{O_2}$ is reduced from a high value they *keep $\dot{M}_{O_2}$ constant* until a critically low $\dot{T}_{O_2}$ value is reached, a phenomenon that was described more than twenty years ago by Stainsby and Otis[6]. Since then it has usually been assumed that

physiological resting-state $\dot{M}_{O_2}$ corresponds to the plateau value of O_2-regulating preparations [13].

High energy costs of maintenance

The question why, at high $\dot{T}_{O_2}$, O_2-conforming preparations have higher $\dot{M}_{O_2}$ values than O_2-regulating ones remained unanswered [7], but one possibility is that fewer cells are 'protected' from receiving non-limiting amounts of O_2 and substrates, and therefore more cells maintain high cellular energy potentials at the expense of a high oxidative metabolic rate. This interpretation is supported by the results of Gutierrez et al. (op. cit., fig. 6), showing that the relative phosphocreatine content of muscle tissue tends to be larger in O_2 conformers than in O_2 regulators at arterial P_{O_2} values above 40 Torr. The positive correlation of ATP and glycogen contents with local blood flow found by Franzen et al. [8], studying macroscale heterogeneity in normal myocardium, also supports this view. It should be stressed, however, that macroscale heterogeneity (0.1 to 0.5-g sampling grain), which was first described in skeletal muscle [16, 17], probably has an origin entirely different from that of the more marked – although less easily demonstrated – microscale heterogeneity. The former is present in the working as well as in the resting muscle [12], whereas the latter disappears in a stimulated motor unit, as such a unit seems to be recruited together with its entire supporting vasculature [11]. Microscale heterogeneity or its effects can also be artificially suppressed in a vascularly isolated muscle by perfusing it at high flow rate with a high-P_{O_2} albumin-saline solution (see below).

O_2-conforming nature of cells

Quantitative comparisons of $\dot{M}_{O_2}$ between perfused and nonperfused muscle tissue preparations [19] and between blood-perfused and saline-perfused vascularly isolated muscles [2] suggested that the high $\dot{M}_{O_2}$ of a nonperfused thin muscle preparation in a high-P_{O_2}environment, or of a muscle perfused at high flow rate with a high-P_{O_2} solution in a low-P_{O_2} environment, simply reflects the O_2-conforming nature of cells as opposed to the O_2-regulating behavior of normal, blood-perfused muscles. In saline-perfused muscles where both $\dot{M}_{O_2}$ and heat production rate were measured, comparisons of input and output energy flow rates (indirect and direct caloric fluxes, respectively) showed that a stepwise increase of O_2 availability to cells not only increased oxidative metabolic rate, but increased it more than the output energy flow rate. This indicates that the mean energy state of muscle tissue was progressively readjusted to a higher level after O_2 availability had been increased. Unfortunately, observations were not pursued long enough for a new steady state to be demonstrated (i.e., with input and output energy flow rates still increased but again equal to one another).

Substrate-conforming nature of cells

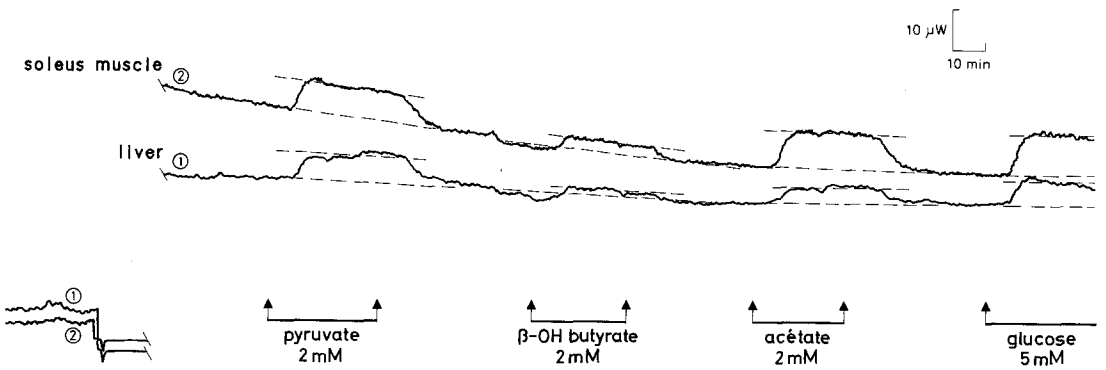
Cell metabolism not only conforms to O_2 availability, it also conforms to substrate availability, and this is not a property of muscle cells only (fig.).

Other indirect evidence

Pharmacological evidence also suggests that the availability of O_2 and substrates to cells may be limited even though deliveries to the organ are not. For example, Takeshita et al. [23] observed that phentolamine produced significant increases of $\dot{M}_{O_2}$ in blood-perfused muscles, but not in superfused muscle strips. Other authors preferred to assume that the increased $\dot{M}_{O_2}$ they observed with constant or increased $\dot{T}_{O_2}$ [7], or even with decreased $\dot{T}_{O_2}$ under the effect of noradrenaline [13], reflected a primary increase of cell metabolism.

How muscles regulate their respiration

Any attempt to explain how muscles regulate their respiration usually starts with the choice of some theory of the control of cell respiration, and then goes on to figure out how the massive and variable flow of oxygen to mitochondria is achieved at a near-constant partial pressure



Influence of various exogenous substrates on the rate of heat production, as a function of time, by two tissue-cell preparations (a soleus muscle and a liver slice from a 65-g rat) superfused with a Krebs-Ringer, bicarbonate-buffered solution at 30 °C in a heat-flux microcalorimeter. Substrates were added to the high-P_{O_2} superfusate at the concentrations and during the time indicated. Baselines are shown in the lower left corner, power and time calibrations in the upper right one. (Redrawn from the original record.)

of oxygen in the sarcoplasm (volume-average P_{O_2} near 3 Torr)[24]. As has already been suggested, however, such an explanation may not hold for muscle at rest where, on the contrary, respiration may normally be controlled by the availability of O_2 (and substrates) to cells. In other words, this extrinsic component of control must be taken into account in biochemical models of cellular respiratory control, together with the various elements usually considered (i.e., changes in the cytosolic phosphate energy state, in intracellular pH, in the adenine nucleotide or phosphate pools, in intramitochondrial calcium activity, etc.). True, phosphate energetics and/or regulation via calcium-modulated enzyme activities in the mitochondrial matrix[15] may account for most of the $\dot{M}_{O_2}$ variability in the working muscle, where an independent redox component may be small[3] and availability of O_2[9,18] and substrates[25] are probably not limiting factors. However, an entirely different type of control, that is, extrinsic control via O_2 and substrate availability to cells, might prevail in the unstimulated motor unit.

The cell in a stationary state: An overall non-equilibrium catalyst modulated by substrates and products

An interesting implication of extrinsic control of respiration is that the cell in a stationary state can no longer be considered an overall catalyst unaffected by substrates or products, whose intrinsic properties rigidly determine the rate of substrate-to-end-product reactions. Indeed, the cell as a non-equilibrium catalyst of metabolic reactions during steady states is itself modulated by the presence of substrates and products. Increased substrate availability and/or clearance of products will bring the overall catalyst further out of equilibrium, with the consequence that the rate of substrate-to-end-product reactions will have to be larger in the new stationary state of the cell. The mechanisms of such increases in 'budget expenses', where offer creates demand, are only partially understood, and the relative roles of O_2 and substrates have not been quantified. What can be said is that an increase in the availability of substrates and O_2 can not only increase ion recirculations across inner mitochondrial membranes and increase the activity of key enzymes in the Krebs cycle[1,21,22], but is also likely to increase cell protein turnover. Sensitivity of skeletal muscle proteasomes to ATP concentrations in the physiological domain has recently been demonstrated[5].

Conclusion

Available evidence suggests that *muscle cell respiration at rest undergoes physiological control by the organ* in that the organ normally restrains the access of O_2 and substrate to its cells, even if it is obtaining non-limiting O_2 and substrate deliveries.

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