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Why are skeletal muscles not depleted of energy during intense exercise?

ATP is a universal carrier of energy in a form easily accessible for different reactions in the cell. Its hydrolysis to ADP and P_i (inorganic phosphate) drives processes that cannot occur spontaneously and require energy, for instance muscle contraction. The main processes hydrolyzing ATP during muscle work are actomyosin-ATPase that uses ATP for relative movement of myosin and actin filaments related to muscle shortening, while Ca^{2+}-ATPase (SERCA) pumps Ca^{2+} to sarcoplasmic reticulum against electrochemical gradient (release of Ca^{2+} from reticulum is the signal for muscle contraction, while its backward taking up enables muscle relaxation). The main source of ATP in intense, lasting several minutes exercise is oxidative phosphorylation (OXPHOS) in mitochondria. It is carried out by a few protein complexes located in the inner mitochondrial membrane. Three of these complexes (complex I, complex III and complex IV = cytochrome oxidase) are proton pumps that transfer H^+ ions (protons) outside mitochondria, which is driven by electron flow from NADH to oxygen, thus creating electroosmotic gradient. ATP synthase uses this gradient for ATP synthesis, while ATP/ADP carrier and P_i carrier: for transport of ATP outside mitochondria, and ADP and P_i inside mitochondria.

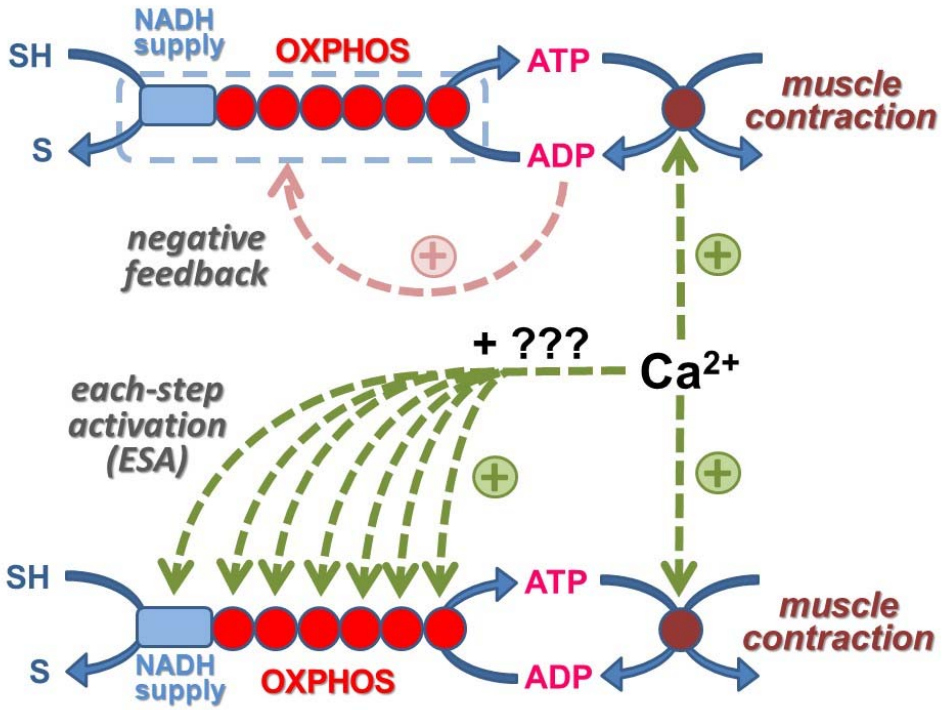

Fig. 1. Comparison of two possible mechanisms of the regulation of oxidative phosphorylation (OXPHOS) during work transitions in muscle. S, oxidized substrate; SH, reduced substrate.

The activity of ATP usage in skeletal muscle can increase over 100-fold during rest-to-intense-work transition. ATP supply must quickly match ATP demand, otherwise ATP would be completely depleted in a couple of seconds and muscle cell would stop to work. According to the traditional view based on the studies on the regulation of OXPHOS in isolated mitochondria by Chance and Williams, only ATP usage is directly activated by Ca^{2+} during muscle contraction, which leads to ATP hydrolysis to ADP and P_i, while ATP synthesis by OXPHOS is activated only indirectly, through the negative feedback involving an increase in ADP (and P_i) (Fig. 1, upper panel).

However, theoretical studies carried out using a broadly validated computer model of OXPHOS and the entire muscle bioenergetic system strongly suggest that this mechanism is decidedly insufficient to avoid a quick depletion of ATP. Theoretical studies led to the conclusion that not only ATP usage, but also other components of the system, namely all OXPHOS complexes, NADH supply block (tricarboxylic acid cycle, malate-aspartate shuttle, fatty acid oxidation) and glycolysis must be directly activated by some cytosolic factor related to muscle contraction (Fig. 1, lower panel) in order to account for numerous system properties encountered in experimental studies.

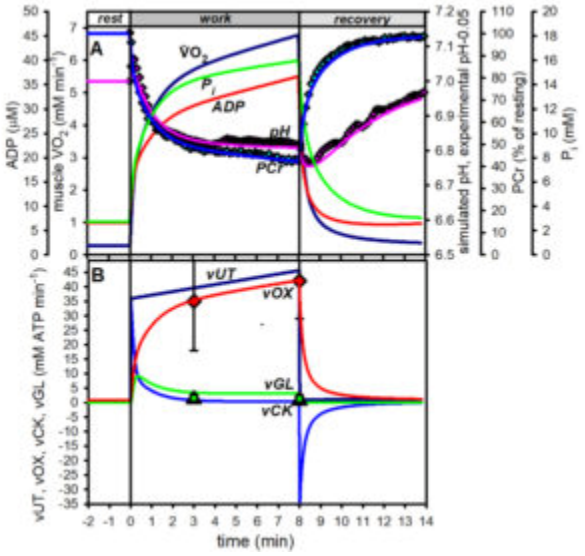

Fig. 2. Comparison of experimental (points) and simulated (lines) time courses of muscle bioenergetic system variables during rest → intense work → recovery transition in human skeletal muscle. vUT, ATP usage; vOX, ATP supply by OXPHOS; vCK, ATP supply by creatine kinase; vGL, ATP supply by anaerobic glycolysis.

This mechanism has been named each-step activation (ESA). The mentioned system properties comprise, among others: much greater oxygen consumption ($\dot{V}O_2$) and ATP turnover in intensively working muscle than in isolated mitochondria, very moderate changes in metabolite levels: ADP, PCr (phosphocreatine), P_i and ATP during work transitions, and uniform distribution of metabolic control over $\dot{V}O_2$ among OXPHOS complexes. The model involving the ESA mechanism is able to explain many, apparently not related to each other, properties of the system (see e.g., Fig. 2). It was proposed that ESA is also the main mechanism of the bioenergetic system (including OXPHOS)

regulation in heart, where essentially no changes in metabolite concentrations take place during work transitions. The factor/mechanism responsible for the direct activation of particular system elements is not known. It has been proposed that it involves Ca^{2+} and calmodulin-like protein that binds calcium ions and activates different proteins through phosphorylation.

Therefore, the model offers a unique opportunity to predict the existence of new, still not discovered phenomena. Of course, this prediction will have to be verified or falsified in the experimental way.

Bernard Korzeniewski
Faculty of Biochemistry, Biophysics and Biotechnology, Jagiellonian University, Kraków, Poland

Publications

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