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Regulation of oxidative phosphorylation through each-step activation (ESA): Evidences from computer modeling

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ABSTRACT

The mechanisms responsible for matching of the highly varying ATP demand by ATP supply in muscle are of primary importance for pure science, sport science and medicine. According to the traditional opinion ATP supply is activated by elevated ADP and P_i resulting from ATP hydrolysis during intensive work. Theoretical studies using the computer model of oxidative phosphorylation (OXPHOS) and the entire cell bioenergetic system developed by the author and co-workers lead to the each-step-activation (ESA) mechanism of the regulation of the system in skeletal muscle, heart and other tissues during work transitions. According to ESA not only ATP usage, but also all OXPHOS complexes (complex I, complex III, complex IV, ATP synthase, ATP/ADP carrier, P_i carrier), NADH supply block and (anaerobic) glycolysis are directly activated by some cytosolic factor/mechanism during rest- or low-to-high work transitions. ESA conception results from large increase in oxygen consumption ($\dot{V}O_2$) and ATP turnover flux accompanied by only moderate or no changes in metabolite (ADP, P_i, PCr, NADH) concentrations during work transitions in skeletal muscle and heart and from the uniform distribution among OXPHOS complexes of the metabolic control over $\dot{V}O_2$, as defined within Metabolic Control Analysis. Several theoretical studies carried out using the discussed computer model of the cell bioenergetic system are overviewed. It is demonstrated that this model, involving the ESA mechanism, is able to explain numerous, apparently unrelated to each other, properties of the system.

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Abbreviations: A_{DH}, relative activation of NADH supply (times) (increase in its rate constant) in relation to rest; A_{GL}, relative activation of glycolysis (times) (increase in its rate constant) in relation to rest; A_{OX}, relative activation of OXPHOS (times) (increase in rate constants of all its complexes) in relation to rest; A_{UT}, relative activation of ATP usage (times) (increase in its rate constant) in relation to rest; AK, adenylate kinase; CK, creatine kinase; ESA, each-step activation; OXPHOS, oxidative phosphorylation; $t_{1/2on}$, half-transition time during on-transient; $t_{1/2off}$, half-transition time during off-transient; $t(ON)_{DH}$, characteristic activation time of NADH supply during on-transient; $t(ON)_{GL}$, characteristic activation time of glycolysis during on-transient; $t(ON)_{OX}$, characteristic activation time of OXPHOS during on-transient; $t(OFF)_{DH}$, characteristic inactivation time of NADH supply during off-transient; $t(OFF)_{GL}$, characteristic inactivation time of glycolysis during off-transient; $t(OFF)_{OX}$, characteristic inactivation (decay) time of OXPHOS during off-transient; vCK, rate of ATP synthesis by CK; vGL, rate of ATP synthesis by anaerobic glycolysis; vOX, rate of ATP synthesis by OXPHOS (+aerobic glycolysis); vUT, the rate of ATP utilization; $\dot{V}O_2$, rate of oxygen consumption.

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1. Introduction

1.1. Excitable cell bioenergetic system

The basic mechanism of ATP synthesis by oxidative phosphorylation is known since Mitchell proposed the chemiosmotic theory (Mitchell, 1961). However, the regulation of OXPHOS and the entire cell bioenergetic system during work transitions in different tissues, in particular during rest-to-work transition in skeletal muscle and low-to-high work transition in heart is still not fully understood. The cell bioenergetic system in excitable tissues/organs (heart, skeletal muscle, brain) is composed of OXPHOS complexes (complex I, complex II, complex III, complex IV, ATP synthase, ATP/ADP carrier, P_i carrier), NADH supply block (tricarboxilic acid (TCA) cycle, fatty acids β-oxidation, malate/aspartate shuttle (MAS), substrate transport), (aerobic + anaerobic) glycolysis + glycogenolysis, ATP usage (actomyosin-ATPase, Ca^{2+}-ATPase, Na^+/K^+-ATPase, basal ATP usage reactions such as protein or nucleic acid synthesis), creatine kinase (CK) system, proton leak through the inner mitochondrial membrane, proton efflux/influx from/to cytosol to/from blood. The cell bioenergetic system containing the enumerated components is depicted in Fig. 1. It shows the elements of the system that are taken into account explicitly within the computer model discussed in the present review/polemic article (complex II and FAD are omitted for simplicity and because they are not taken into account explicitly in discussed computer model).

In the present article ATP, ADP, P_i and pH design cytosolic ATP, ADP, P_i and pH, while NADH designs mitochondrial NADH, unless stated otherwise. PCr and AMP are exclusively cytosolic.

1.2. Mechanisms/models of the regulation of the cell bioenergetic system during work transitions

Several mechanisms and (computer) models describing the regulation of oxidative phosphorylation and the whole mammalian cell bioenergetic system (especially in skeletal muscle and heart) were proposed/developed.

According to the first mechanism/simple model, originally inspired by the discovery by Chance and Williams (1955, 1956) of the activation of oxidative phosphorylation in isolated mitochondria by ADP, only ATP usage is directly activated by Ca^{2+} in the result of external cell stimulation (e.g., by neural stimulation or hormones), while OXPHOS and the entire ATP-supply block is activated only indirectly, through an increase in the concentrations of ATP hydrolysis products: ADP and P_i. In isolated mitochondria, where P_i concentration is usually maintained on a high, (approximately) constant level, ADP is essentially the only activator of OXPHOS. Its concentration can be imposed either by addition of determined external amount of ADP to the incubation medium, or by setting of an appropriate activity/concentration of an artificial ATP consumption system, usually hexokinase in the presence of glucose and ATP. In intact skeletal muscle P_i cooperates with ADP in stimulation of OXPHOS and the entire cell bioenergetic system during elevated ATP demand. However, its role seems to be smaller than ADP, because, at physiological concentrations (e.g., at rest or low work), OXPHOS is more saturated with P_i than with ADP: compare e.g., the apparent K_m ($K_{1/2}$) for ADP (Gouspillou et al., 2011) and P_i (Bose et al., 2003) with the values of ADP and P_i at rest and during work in skeletal muscle (Hogan et al., 1992). Therefore, the increase in ADP stimulates OXPHOS to a greater extent than the increase in P_i during rest-to-work transition (Liguzinski and Korzeniewski, 2006). As it is discussed below, essentially no changes in ADP and P_i take place during work transitions in intact heart *in vivo*. The static (not involving changes in time) model developed by Bohnensack (1981) also assumed only the activation of OXPHOS by ADP and P_i. This mechanism can be called 'negative-feedback activation' or 'output-activation' mechanism (Korzeniewski, 2007, 2014), as only ATP usage, the output of the system, is directly activated. Usually a hyperbolic (Michaelis-Menten-like) $\dot{V}O_2$–ADP dependence is observed in isolated mitochondria (Gouspillou et al., 2011). On the other hand, it was postulated by Jeneson and co-workers on the basis of the steep phenomenological ATP synthesis-ADP relationship observed in human skeletal muscle during increasing work intensity that the mechanistic $\dot{V}O_2$–ADP (and oxidative ATP synthesis (vOX)-ADP)