

Komlodi 2017 Abstract MITOEAGLE Barcelona

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Succinate dehydrogenase regulation via oxaloacetate in brain mitochondria.

Link: MITOEAGLE

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Abstract in preparation:

Succinate dehydrogenase (SDH or Complex II) is the only enzyme participating both in the electron transfer system (ETS) and the tricarboxylic acid cycle (TCA cycle). Succinate is generated by the TCA cycle in the mt-matrix, and cytosolic succinate plays additional metabolic roles, participating in hypoxia-induced cellular reactions and tumorigenesis [1].

Succinate without the Complex I inhibitor rotenone is well known to induce high levels of H_2O_2 production, which is suggested to be of pathophysiological significance in ischemia-reperfusion injury [2]. The aim of the present study was to investigate the organ- and species-specific regulation of respiration and hydrogen peroxide production in the succinate pathway in view of an ADP-induced respiratory depression observed in some tissues.

Experiments were carried out on (i) isolated mitochondria of guinea pig brain, kidney, liver and heart, and (ii) isolated mitochondria or homogenate of mouse cardiac tissue. Mitochondrial respiration was measured by high-resolution respirometry (OROBOROS, Innsbruck, Austria). O₂k-Fluorometry was applied to the mouse mitochondria for simultaneous measurement of respiration and H_2O_2 production. In the guinea pig tissues, H_2O_2 production was measured separately by spectrofluorometry (Photon Technology International, Lawrenceville, NJ). SDH, malic enzyme, phosphoenolpyruvate-carboxykinase (PEPCK) and hydroxy-oxoglutarate aldolase (HOGA) [3] enzyme activities were determined by spectrophotometry (ABL&E-JASCO V-650, Tokyo, Japan) in brain and kidney tissue.

In all tissues, H_2O_2 production was much higher with S(-Rot) than S(+Rot) in the absence of ADP (LEAK state). ADP (2 mM) added to S(+Rot) increased respiration from the LEAK to the OXPHOS state. Surprisingly, however, ADP added to S(-Rot) inhibited oxygen consumption with respect to the LEAK state at low succinate concentration in guinea pig brain and heart, but even at high (10 mM) succinate concentration in mouse heart. This so-called "succinate paradox" was not observed in guinea pig liver and kidney. H_2O_2 production generally declined to low levels after addition of ADP in states S(+Rot) and S(-Rot). The response of NADH to addition of ADP was diametrically different for S(-Rot) (decrease of NADH) and S(+Rot) (increase of NADH) in mouse cardiac tissue.

SDH (CII) is inhibited by endogenously produced oxaloacetate (Oa), which is particularly pronounced in state S(-Rot) [4]. However, exogenously added Oa inhibited SDH measured in brain and kidney, independent of the succinate paradox [5,6]. Addition of rotenone, pyruvate or glutamate abolished the respiration inhibition, because rotenone decreased Oa production and pyruvate or glutamate increased Oa elimination. Addition of malic enzyme to isolated guinea pig mitochondria decreased the concentrations of malate and increased the pyruvate concentration, respectively. Measuring HOGA and PEPCK enzyme activity we can draw the conclusion that PEPCK and HOGA activity was higher in kidney than in brain mitochondria.

The cause of organ specificity of ADP-mediated inhibition of succinate respiration could be different mechanisms and efficacies of OA elimination. Our results showed that PEPCK and HOGA enzymes take part in the regulation of OA concentration, which is the main metabolic inhibitor of SDH [6]. Elevated production of H₂O₂ in the LEAK state can be attributed to succinate-driven reverse electron transfer towards CI which was inhibited by rotenone even at low concentrations of succinate.

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Labels: **MiParea**: Respiration

Organism: Mouse, Guinea pig **Tissue;cell**: Heart, Nervous system, Liver, Kidney **Preparation**: Homogenate, Isolated mitochondria **Enzyme**: Complex II;succinate dehydrogenase, TCA cycle and matrix dehydrogenases **Regulation**: ADP, mt-Membrane potential, Substrate **Coupling state**: LEAK, OXPHOS, ETS **Pathway**: N, S **HRR**: Oxygraph-2k, O2k-Fluorometer **Event**: B3

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