Rutter, G. A., McCormack, J. G., Halestrap, A. P., & Denton, R. M. (2020). The roles of cytosolic and intramitochondrial Ca2+ and the mitochondrial Ca2+-uniporter (MCU) in the stimulation of mammalian oxidative phosphorylation. *Journal of Biological Chemistry*, *(2020) 295*(30), 10506-10506. https://doi.org/10.1074/jbc.L120.013975

JBC/2020/013975.R1

The roles of cytosolic and intramitochondrial Ca^{2+} and the mitochondrial Ca^{2+}-uniporter (MCU) in the stimulation of mammalian oxidative phosphorylation

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Szibor et al. (1) conclude that cytosolic [Ca^{2+}] ([Ca^{2+}]$_{cyt}$) activation of the malate-aspartate shuttle is more important than mitochondrial [Ca^{2+}] ([Ca^{2+}]$_{mit}$) activation of intramitochondrial dehydrogenases in the regulation of pyruvate oxidation by mammalian mitochondria. However, the authors employed unphysiological conditions with isolated mitochondria (saturating ADP), with synaptosomes, thymocytes and fibroblasts (uncoupler and high pyruvate) and with perfused hearts (high pyruvate) that would inevitably deliver the results obtained. Pyruvate dehydrogenase (PDH) activity is largely determined by the ratio of active non-phosphorylated PDH to inactive phosphorylated PDH (PDHP); this ratio depends on the activities of the ATP-linked PDH kinase

(inhibited by ADP and pyruvate), and PDHP phosphatase (activated by $[Ca^{2+}]_{mit}$) (2). Under all the conditions used by Szibor et al. (1), we would predict PDH/PDHP to be so high that further activation by increased $[Ca^{2+}]_{mit}$ is very limited. No measurements of PDH/PDHP ratios were reported. Under physiologically-appropriate conditions, where PDH/PDHP ratios are lower, there is extensive evidence that $[Ca^{2+}]_{mit}$ is an important determinant of pyruvate oxidation (3-5).

Regulation of the malate-aspartate shuttle by $[Ca^{2+}]_{cyt}$ (allowing increased mitochondrial oxidation of cytoplasmic NADH) complements the regulation of intramitochondrial dehydrogenases by $[Ca^{2+}]_{mit}$ (2). We regard the latter as an evolutionary refinement of "intrinsic" mechanisms (also present in lower organisms) enabling increased ATP supply without lowering ATP/ADP ratios (2). Indeed, the MCU blocker ruthenium red decreases ATP/ADP ratios in stimulated hearts (6). The intrinsic mechanisms may operate in MCU-null mice, but these mice do show exercise abnormalities (7). Furthermore, mitochondrial Ca^{2+} influx is not completely suppressed by MCU deletion (7).

254 words including reference numbers

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