Reply to Rutter et al.: 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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Each model used in the work referred to by Rutter et al. (1) addressed certain aspects of mitochondrial biology, and together, they fully support the conclusions made. Please note that we describe Ca$^{2+}$-mediated regulation of oxidative phosphorylation (OXPHOS) fluxes (2, 3) and do not question Ca$^{2+}$-responsiveness of pyruvate dehydrogenase enzyme activity (4). To address concerns such as those raised by Rutter et al. (1), we studied glutamate/malate-dependent OXPHOS in the absence of exogenous pyruvate in mitochondria, omitted pyruvate from cell experiments, and implemented the working rat heart model perfused by Krebs–Henseleit (glucose) buffer. This unequivocally demonstrates in a broad range of models that MAS (malate-aspartate shuttle) inhibition induces a state of mitochondrial pyruvate starvation (3).

An unresolved observation is that mitochondria of MCU knockout mice show negligible activity of Ca$^{2+}$-uptake (5), which we confirm (3). We attributed this activity to residual expression of wild-type Mcu transcripts (3) as the result of a rare event of gene-trap excision during mRNA splicing, since this activity was sensitive to ruthenium red, an inhibitor of the mitochondrial Ca$^{2+}$-uniporter (MCU) in the stimulation of mammalian oxidative phosphorylation. J. Biol. Chem. 295, 10506–10506


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