Comment to the Editor

Metabolic Fluxes and Stoichiometry of Glucose Metabolism

I would like to comment on a recent article by Bertram et al. titled "Interaction of Glycolysis and Mitochondrial Respiration in Metabolic Oscillations of Pancreatic Islets" (1).

The article addresses two different types of oscillations of the membrane potential V and of $[Ca^{2+}]_c$, which are known to occur in the β-cells of pancreatic islets: fast electrical and slow glycolytic oscillations, and fast oscillations superimposed on slow ones (compound bursting). For this purpose, the authors modeled oxidative glucose metabolism of the β-cell (without lactate production). For glycolytic reactions, modified equations of Smolen (2) were applied, whereas for oxidative phosphorylation, a simplified M-K model (Magnus and Keizer (3)) was used. These new equations of glucose metabolism were combined with an earlier model published in 2004 (4), which contains V, $[Ca^{2+}]_c$, $[Ca^{2+}]_{ER}$, and $[ADP]_c$ as main variables. The underlying idea obviously was to show how phosphofructokinase (PFK, M-type)-driven glycolytic oscillations might interfere with oscillations of primarily V and $[Ca^{2+}]_c$. Their results show that the M-type PFK reaction is crucial for glycolytic oscillations, which, however, can be induced only at moderate values of J_{GK}. When M-type PFK is reduced to 30% of total PFK, glycolytic oscillations are not possible and fast oscillations of $[Ca^{2+}]_c$ prevail at $J_{GK} > 0.2$.

These results are not convincing, because the stoichiometry of oxidative glucose metabolism (in a given time interval, 6.0 mol of O_2 are needed to form 6.0 mol of CO_2 with 6.0 mol of H_2O per mole of glucose utilized) is violated. The flux ratio, J_O/J_{GK}, deviates markedly from 6.0. In the relevant article, J_O/J_{GK} is only $\sim$0.76 (conditions of Fig. 2), 1.2 (Fig. 4), or 1.1 (Fig. 6). When these flux ratios were calculated, it was assumed that the mitochondria/cytosol volume ratio $(\kappa = 0.07)$ was already included in calculations; if not, the above values would become reduced by a factor of 0.07.

The following may argue against PFK-driven oscillations of glycolysis in β-cells: the PFK reaction can produce oscillations through a positive feed back of the products ADP (AMP) and fructose 1,6 bisphosphate concentration on enzyme catalytic activity. In the cytosol of the β-cell, however, most of $[ADP]_c$ produced originates from parallel, ATP-coupled reactions such as protein biosynthesis, insulin secretion, and ion transport. The PFK reaction consumes only $\sim$3.8% (5) of total ATP, which stems mainly from mitochondria and to a minor part from glycolysis (7.6% (5)). The kinetics of this large fraction of nonglycolytically produced ADP may control PFK and in this way may induce forced oscillations of glycolysis.

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