Comment to the Editor

Response to the Comment by F. Diederichs

The correspondent has correctly identified that our (1) model is not a biochemically complete description of β-cell metabolism. In particular, there is a phenomenological bridge between glycolysis and the electron transport chain, as we have not modeled all the steps of glycolysis or most steps of the citric acid cycle. The stoichiometric relationships between carbon, hydrogen, and oxygen are therefore not preserved. The study's reviewer's comments led us to reexamine the fluxes, and we found that the ratio J_O/J_{GK} actually ranges from ~53 to 84 in the figures cited, which we agree is implausibly large. The flux of oxygen is in terms of mitochondrial volume, which means it must be multiplied by 0.07, the ratio of mitochondrial/cytosolic volume, to be compared to the glucokinase flux. However, the glucokinase flux is erroneously listed as having units of μM/ms, when it really was μM/s in the computer code, as well as previously published studies using this model component. Thus, the value needs to be multiplied by 1000.

We believe that the metabolic fluxes could be rebalanced without changing the predictions of the model, and that the rebalancing should come about naturally when the citric acid cycle is incorporated into the model. We point out that mass can enter or exit the pathway from glycolysis to respiration at various points, and a ratio of 6 does not consider respiratory control, so that the true balance would have to be determined experimentally, rather than from first principles. Indeed, an experiment using cultured islets showed that glucose oxidation saturates even though its utilization continues to increase when the glucose concentration is increased (2), so the ratio of oxidation to glucokinase rates can evidently differ from the ideal value of 6.

The fundamental hypothesis of our model is that glycolytic oscillations mediated by the positive feedback of fructose 1,6 bisphosphate onto phosphofructokinase are the main driver of slow calcium oscillations in pancreatic β-cells. The correspondent's argument that the feedback of ADP or ATP onto phosphofructokinase is unlikely to be able to drive glycolytic oscillations is thus irrelevant, as this was not what we proposed. His competing model excludes our mechanism by assumption (3). More broadly, our model proposes that the fast oscillations observed are ionic, whereas the slow oscillations are metabolic, such that the two can interact to produce compound oscillations, consisting of episodes of bursts separated by long periods of silence, or ''accordion'' oscillations, which consist of fast bursts with a slowly modulated duty cycle. No other islet model currently can account for such a large number of dynamic behaviors that have been observed in islets. Our model also predicted conditions in which slow oscillations could occur in the absence of fast oscillations, which has also been experimentally confirmed (4). Whereas a more complete model that captures the stoichiometry between glycolysis and respiration would ultimately be desirable, we suggest that the relative explanatory power and differential predictions are more critical for evaluating models in the immediate term.

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