Response to Comment on: Allister et al. UCP2 Regulates the Glucagon Response to Fasting and Starvation. Diabetes 2013;62:1623–1633

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We thank Dr. Gylfe (1) for his interest in our work showing a role for uncoupling protein 2 (UCP2) in regulating α-cell glucagon secretion and suggesting that this is an interesting and potentially important finding. We agree that the role and mechanism of glucose sensing in α-cells is still highly controversial and that two opposing models are promoted in the literature. Our data suggests that the presence of UCP2 in α-cells may play a role in glucose sensing because the absence of UCP2 impaired the release of glucagon, and this was accompanied by reduced mitochondrial membrane potential hyperpolarization, increased reactive oxygen species production, more depolarized plasma membrane potential, and lower intracellular calcium levels. So although the objective of this study was not to define the mechanisms of glucose-regulated glucagon secretion in control cells, but rather to investigate the impact of UCP2 on α-cell function, we have attempted to fit our data into the published models. The first model was suggested by Dr. Gylfe and is based on the role of glucose as an activator of Ca^{2+} sequestration in the endoplasmic reticulum, which inhibits glucagon secretion (2,3). This model also suggests a depolarizing effect of low glucose concentration on α-cell plasma membrane potential (2,4,5). The second model (by Rorsman and colleagues [6]) describes regulation of glucagon secretion by an ATP-sensitive potassium channel–dependent pathway. This model predicts that glucose metabolism increases intracellular ATP, closing ATP-sensitive potassium channels. The channel closure depolarizes α-cell membrane potential to a level that inactivates Na^{+} and Ca^{2+} ion channels, thereby reducing glucagon secretion (7). In our study, we present data that fits with both models. The glucose-induced changes in membrane potential recorded in isolated dispersed α-cells fit with the first model; we show that low glucose concentration caused depolarization and increased intracellular calcium levels along with enhanced secretion. However, the α-cell–specific UCP2 knockout mouse α-cells were more depolarized under both high and low glucose concentrations and secreted less glucagon, which fits with the model by Rorsman and colleagues. In addition, our data show that low-dose diazoxide (1μmol/L), which should hyperpolarize the membrane, increased glucagon secretion under high glucose conditions in control α-cells and could enhance glucagon secretion to control levels in the absence of UCP2. Again these data are in line with the second model of glucagon secretion and perhaps point to the α-cell being secretory within a narrow range of plasma membrane potentials. There may be differences in the data based on the use of dispersed versus whole islets, which were used for the electrophysiological and secretion experiments, respectively. Complex factors such as release of paracrine molecules can regulate glucagon secretion and may play a role in the whole islets studies. In addition, it cannot be ignored that the elevated reactive oxygen species levels (even under low glucose conditions) in the α-cell–specific UCP2 knockout mouse islets could potentially be affecting secretion via a channel-independent mechanism, and this area deserves more investigation. However, as pointed out by Dr. Gylfe, in the context of normal α-cells, low glucose in our hands caused depolarization.

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No potential conflicts of interest relevant to this article were reported.

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