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Using α-cell–specific knockout of the mitochondrial uncoupling protein 2 (UCP2), Allister et al. (1) recently provided evidence for involvement of this protein in glucose regulation of glucagon release. This is an interesting and potentially important contribution with regard to the possible involvement of UCP2. However, the authors do not seem to notice that their data contradict the promoted model. The study focuses on intrinsic regulation of secretion, implying that the α-cell senses the glucose concentration and releases glucagon accordingly. The mechanism for α-cell glucose sensing is controversial, but the authors only mention the most cited model, in which glucose-derived ATP closes ATP-sensitive K⁺ channels to depolarize the α-cell (2). The depolarization leads to inactivation of Na⁺ channels involved in action potential firing and thereby to inhibition of glucagon release. Other α-cell models instead predict that glucose inhibits glucagon secretion by hyperpolarizing the α-cell after activating the electrogenic Na⁺/K⁺ pump (3) or shutting off a depolarizing store-operated current by stimulating Ca²⁺ sequestration in the endoplasmic reticulum (4,5).

Surprisingly, it is not settled how glucose affects the membrane potential of α-cells. Whereas electrophysiological recordings have indicated both depolarizing (2) and hyperpolarizing (6) effects, noninvasive measurements with a potential-sensitive dye indicate that glucose elevation hyperpolarizes α-cells (4,7). Using the electrophysiological approach, Allister et al. provide additional evidence for a hyperpolarizing effect of glucose both in control and UCP2-knockout α-cells. However, this finding is never mentioned. Focus is instead on UCP2-knockout α-cells being more depolarized, which is assumed to reflect higher ATP production. It seems somewhat biased to highlight indirect indications of metabolism-mediated depolarization of the α-cell and suppress direct evidence for a hyperpolarizing effect of glucose that contradicts the favored model for glucagon secretion.

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REFERENCES

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