The right stuff: β-cell channels, cycles, and sensors

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The vast majority of the 200 million or so individuals with diabetes worldwide suffer from type 2 diabetes, with relative insulin deficiency arising from the failure of β-cells to compensate for the prevailing insulin resistance. Indeed, it is the combination of impaired β-cell function and decreased β-cell mass that underlies the progression from insulin resistance with normal glucose tolerance toward clinically manifested diabetes (11). Understanding the mechanism and regulation of insulin secretion in fine molecular detail may lead to the identification of new drug targets for type 2 diabetes. This is the focus of the three review articles in this issue of the American Journal of Physiology - Endocrinology and Metabolism. Written by acknowledged leaders in the field, they are not intended to be all embracing but rather to update us on today’s understanding of the molecules and events underlying three specific facets of the regulation of insulin secretion by glucose. As we learn more about neuroendocrine cells in general and the β-cell in particular, the more obvious it becomes that characterizing the “right stuff” that underlies their exquisitely well-differentiated state will be one of the great challenges of contemporary cell biology. Forty years after publication of the method for isolating pancreatic islets that allowed for the in vitro study of β-cells and insulin secretion (12), we are still discovering major new molecular players as we continue to unravel the mysteries of this enigmatic cell. At the same time, genome-wide association studies are providing insight into the genetic basis of type 2 diabetes, placing the spotlight squarely on the β-cell (6).

It has been known for many years that glucose stimulus-secretion coupling depends on metabolism of the sugar. Historically, the resulting rise in the ATP/ADP ratio was considered the major if not the only metabolic signal, closing ATP-sensitive K⁺ (KATP) channels, triggering a cascade of electrophysiological events, increasing cytosolic Ca²⁺, and ultimately stimulating exocytosis. But this is by no means the whole story. The (often lonesome) work of pioneers such as Jean-Claude Henquin indicated the profound effect of other metabolizable substrates on this process and was one of the early players in the “calcium game” (14). Showing his tenacity, Wollheim revisits this theme of glucose stimulus-secretion coupling, this review article offers an accessible yet impressive refresher course in carbohydrate metabolism. The search for the remaining elusive metabolic factors that potentiate glucose stimulus-secretion coupling continues, and the authors conclude with a challenging “to-do” list that rightly includes repeating some of the key experiments using human islets.

Regardless of the proximal metabolic or ionic events discussed above, our understanding of glucose stimulus-secretion coupling would be incomplete without knowing how exocytosis is ultimately increased in response to a rise in cytosolic Ca²⁺. The exocytotic machinery of the β-cell is no longer a black box, thanks in major part to the realization that this cell shares many features in common with neuronal cells in which these events have already been better studied. Claes Wollheim has devoted his distinguished academic career to the study of the β-cell and was one of the early players in the “calcium game” (14). Showing his tenacity, Wollheim revisits this theme (7) by focusing on the β-cell calcium sensor. As mentioned repeatedly above, a rise in Ca²⁺ is a prerequisite for glucose-stimulated insulin secretion. But how does this work? How is this rise detected and translated into a signal for increased exocytosis? It would seem as though the elusive calcium sensor has now been identified: synaptotagmin. Gauthier and Woll-
heim provide a concise overview of the exocytotic machinery and home in on this family of proteins. They argue that two isoforms are of particular relevance to calcium sensing in the β-cell (synaptotagmin VII and IX) and they, too, stress the importance of studying primary β-cells rather than transformed cell lines that are typically less well differentiated and present a mixed endocrine cell phenotype.

These three review articles offer a unique glimpse into the rarefied world of the β-cell. This cell continues to fascinate and has certainly not yet shared all its most intimate secrets with us. The research community has been galvanized by the attention the β-cell is receiving from clinicians, geneticists, and the pharmaceutical industry alike. Understanding how the β-cell works in health and how and why it fails or dies in diabetes (whether it be quasi-total autoimmune destruction in type 1 diabetes or decreased functional mass in type 2) may pave the way for new (hopefully improved) treatment and perhaps a cure for diabetes. The development of glucagon-like peptide-1-based therapy for type 2 diabetes is a case study in this regard (5).

REFERENCES