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Emptying the Pool: Modular Insulin Secretion From the Pancreas

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COMMENTARY

The fundamental model of glucose-stimulated insulin secretion has remained essentially unchanged for decades. Rising blood glucose is transported into pancreatic β-cells, where it is metabolized to generate ATP. The change in the ATP/ADP ratio closes membrane potassium channels and eventually triggers the action potential that drives calcium influx and exocytosis. Secreted insulin typically comes from a very small portion of the available secretory granules (<1%) (1,2). This has led to much speculation concerning the vast majority of dormant secretory granules known as the "reserve pool." Does it participate in phasic insulin secretion (3,4)? Is the number of reserve pool granules regulated (5)? And perhaps most importantly, what is the relationship between the reserve capacity and diabetes (6)? That this large unsecreted pool of granules is truly held in reserve has not been a commonly challenged idea and is in fact a part of a core assumption about islets isolated for ex vivo experimentation: Islets are all more or less functionally identical and respond similarly to the environmental changes that regulate secretion. The insulin that is secreted in response to rising blood glucose levels, it is therefore thought, arrives from all islets with each islet secreting a tiny bit of insulin from just a handful of secretory granules at a time.

It is curious then that the β-cells are organized into islets consisting of relatively small numbers of cells ranging from tens to thousands (7,8) as opposed to a monolithic structure like the adrenal medulla (Fig. 1). As an anatomical unit, the modularity of the islets can be quite extensive. Humans have several million islets (9), for example, and this is advantageous in some respects. In evolutionary terms, modularity provides what is known as robustness against perturbations (10). Islets are anatomically disconnected from one another, preventing the spread of damage and dysfunction. Further, damage to a particular group of islets can be compensated for by having other islets pick up the slack. But this raises the question of how the secretory output from millions of islets is coordinated and finely tuned in response to changes in blood glucose. Given the very small margin for error (~2–3 mmol/L) on the hypoglycemic side of the blood glucose set point (11), it is fair to say that this is an open question and one that is not particularly easy to address experimentally using ex vivo preparations.

There are certain questions that can only be answered by physiologic experimentation in a living animal: mapping neuronal circuitry to behavior (12) and regulation of vascular tone (13), to name two. This issue of homeostatic control over insulin secretion seems to be a third (14). Numerous regulatory pathways that may influence insulin secretion (15) have been identified by exposing cultured islets to various biologic agonists, but ex vivo experiments cannot tell us which agents are the most prominent natural regulators in the living organism. Genetic models, such as tissue-specific receptor knockouts, cannot provide definitive evidence for such a naturally robust system without being able to measure secretion from individual islets in vivo.

In this issue of *Diabetes*, Zhu et al. (16) describe intravital imaging of pancreatic islet secretion. This report describes a new mouse model that transgenically expresses a fluorescent cargo labeling the lumen of insulin secretory granules. Importantly, this construct is well tolerated and the mice show no signs of dysfunctional glucose homeostasis. Isolated islets are also normal, and secretion of the cargo was shown to faithfully report insulin secretion. The intravital imaging experiments, however, produced some very surprising results that challenge the presumption that all islets are equal opportunity responders to rising blood glucose levels. First, secretion was observed from only a partial fraction of islets in response to oral or intravenous glucose administration. More surprising was the extent of secretion, with responding islets losing nearly all of their fluorescence cargo in some cases (Fig. 1).

This is a provocative finding from two perspectives. First, there is no known mechanism for stimulating

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See accompanying article, p. 699.

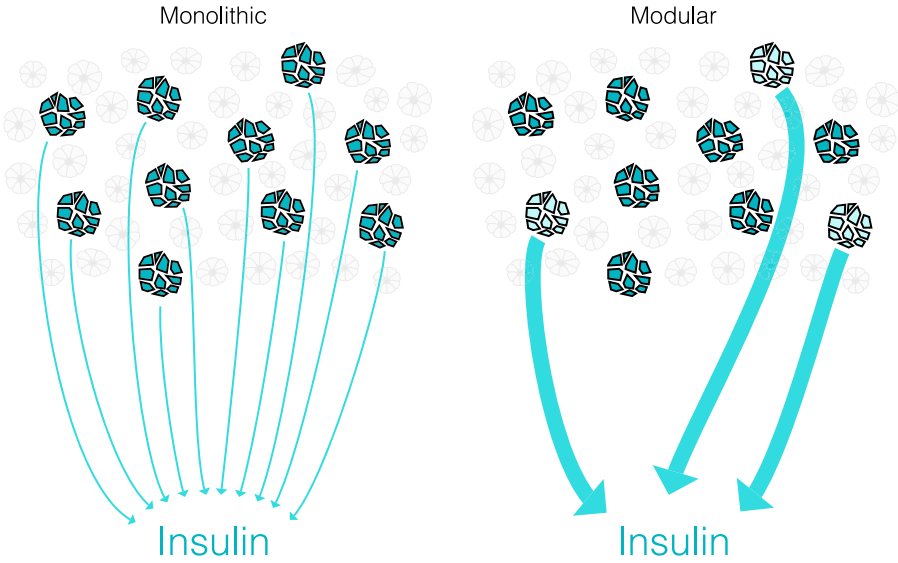

Figure 1—Monolithic versus modular islet secretion. Experiments on cultured islets suggest that each islet has an inherent ability to sense a rise in blood glucose and secrete a small amount of insulin, thus behaving like a monolithic system (left). New evidence from Zhu et al. (16) suggests that secretion may occur in a more modular fashion (right). In this model, select islets secrete a large amount of their cargo in response to rising blood glucose, while the majority of islets remain dormant.

insulin secretion that can seemingly mobilize the entire reserve pool. Clinically useful regulators of insulin secretion, such as the incretins, potentiate secretion approximately twofold (17,18), and the maximum potentiation via extraordinary treatments (e.g., forcibly depolarizing the cell by chemical means) seems to top out at approximately fivefold (19). This falls in line with estimates that a maximum of 5% of the insulin secretory granule pool can be mobilized in vitro (1). However, secretion from "first responder" islets appears to be 10- to 100-fold greater than the maximum in vitro secretory response. Either these islets have a fundamentally different secretory mechanism or some unknown agonist is powerfully augmenting glucose-triggered secretion. Second, these findings suggest that there are potential therapeutic opportunities for agents that drive islet secretion more forcefully, should we be able to identify the underlying molecular mechanisms responsible. Harnessing even a fraction of this potential would be a powerful therapy for early-stage type 2 diabetes.

Future work will surely help us understand the quantitative impact of the first responders in raising blood insulin levels. It is still unclear if the "nonresponders" are actually secreting or not, especially if they are secreting at the rate predicted by ex vivo experiments. A decrease in islet fluorescence by 1% or less would be very difficult to measure by fluorescence microscopy. Secretion that is undetectable by the methods of Zhu et al. (16) could even quantitatively contribute more to the rise in plasma insulin than the first responders, if such low responders are present in overwhelmingly greater numbers. Finally, it is also worth noting that the experimental measurements of Zhu et al. were performed under anesthesia, which is known to alter glucose homeostasis (20). Even so, the findings of Zhu et al. are important because they suggest that the entire pool of granules may in fact be fully tapped under the right conditions and thus may not be entirely "reserved" after all.

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