Sleeping Islets and the Relationship Between β-Cell Mass and Function

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Research will always bring surprises. A study in this issue presents a fascinating new mechanism for how insulin secretion may be more tied to functional than actual β-cell mass. Olsson and Carlsson (1) found 20–25% of islets in normal rat pancreata immunostained for pimonidazole, a hypoxia marker that accumulates in cells with oxygen levels <10 mmHg. They make a good case that these islets secrete less insulin than "normal" islets, which have oxygen tensions of ~40 mmHg. When β-cell mass is decreased with partial pancreatectomy, these dormant islets seem to be called into action. Conversely, when β-cell mass is increased with pancreas transplantation, the number of these pimonidazole-stained sleeping islets increases, suggesting that insulin secretion from a population of islets is no longer needed (Fig. 1).

This study may be another example of how animal studies can identify important new mechanisms in humans. However, does such a phenomenon exist in humans and how important might it be? What does inactivity of islets mean? In rats, it means that there are islets with reduced blood flow and low oxygen tension that presumably secrete less insulin—but how much less per islet and how much less for a pancreas that may contain islets with varying degrees of inactivation?

It is clear that in the face of insulin resistance, glucose levels can be kept in the normal range by increases in pancreatic insulin secretion. This compensation has been thought to be due to enhanced secretion by whatever β-cell mass is present in the short term and subsequent increases in β-cell mass, which provide additional secretion. Certainly, animal studies have supported this concept in that impressive increases in β-cell mass have been found in models of insulin resistance, most notably in rodents (2).

Surprisingly, in humans the concept that increased β-cell mass contributes importantly to the increased insulin secretion found in obese insulin-resistant humans has not found strong support. There are now several autopsy studies indicating that β-cell mass in pancreata of obese individuals is only 20–50% greater than that found in pancreata of lean subjects (3,4). However, rigorous studies of insulin secretory rates show that secretion over 24 h and after meals is more than 100% of that found in lean control subjects (5). These data lead to the conclusion that compensatory insulin secretion is quantitatively more important that a compensatory increase in β-cell mass.

There seem to be two ways that regeneration might take place—through replication of existing β-cells and by the production of new β-cells from neogenesis (6). Remarkably, it is becoming increasingly clear that β-cell replication is truly negligible in most adult humans (7,8), in that thousands of β-cells can be examined using such tools as Ki67, which identifies cells in the cell cycle, with little evidence of replication. The contribution of neogenesis remains a puzzle, but there seems to be a slow process of β-cell death as measured by transferase-mediated dUTP nick-end labeling staining, suggesting that β-cell mass is maintained by slow production of new β-cells. Questions remain about whether neogenesis is an effective mechanism to compensate for insulin resistance.

There has been hope that it might be possible to expand β-cell mass in adults with diabetes through regeneration. This remains an important goal, but it is looking as if there is little regeneration in the face of insulin resistance in most humans. There has also been hope that glucagon-like peptide-1 agonism with or without gastrin or epidermal growth factor would increase β-cell mass, as has been demonstrated in rodents (9). It is still too early to draw firm conclusions, but in spite of the widespread clinical use of agents that lead to activation of glucagon-like peptide-1 receptors, nothing has emerged to suggest they produce an increase in either functional or actual β-cell mass.

Now we have a new mechanism to add to the equation—that there is a reserve pool of islets that can be called into action when needed. Thus, it becomes even more evident that there can be important changes of insulin secretion that occur with no change in β-cell mass. This makes the concept of functional β-cell mass all the more important. We already know that glucose toxicity causes a major reduction in the function of a given mass of β-cells (10). Existing studies suggest that insulin secretion may be cut by 70% or more by glucose toxicity (11). How do we now factor in a new mechanism whereby some islets are inactive but can be called upon as needed?

Obviously, this exciting discovery opens up an array of important questions. What percentage of islets in humans is inactive? How can this be studied? What happens with obesity, pregnancy, wasting illness, starvation, or physical training? How does age influence the process? What controls the activation or inactivation process? Can islets cycle through activation and inactivation, and if so, how often? Is the process age-dependent such that younger islets are more likely to be inactive or vice versa?

There are several interesting situations in which the activation state of islets may play an important role. Pregnancy requires increases insulin secretion, which is in part mediated by increases in β-cell mass. A recent study of autopsied human pancreata found an increase in relative β-cell volume apparently from an increase in small

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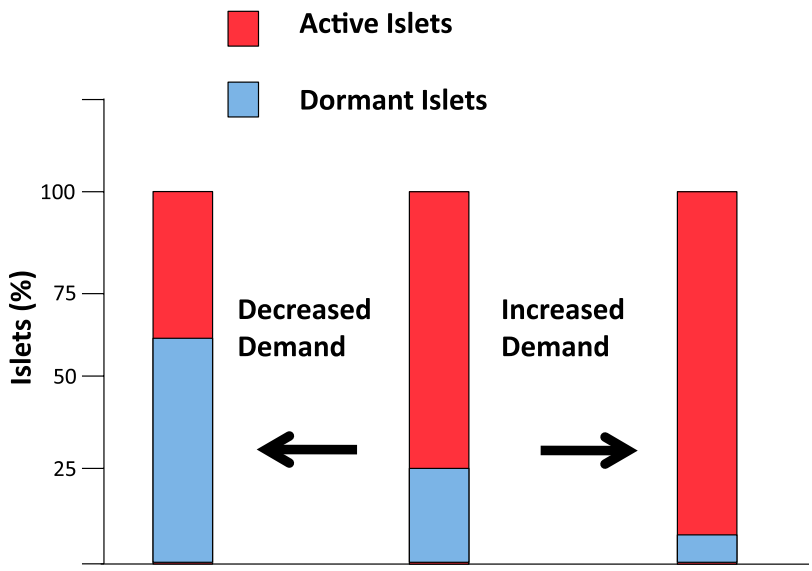

FIG. 1. Hypothesis that dormant islets can be activated by demand. When the pancreas is confronted with increased demand from insulin resistance, dormant islets are recruited into an active state, thus contributing to compensatory insulin secretion. In contrast, with decreased demand, as might occur with exercise and weight loss, some active islets may be shut down to a dormant state.

collections of β-cells throughout the pancreatic parenchyma (12), but perhaps islet activation was also at play. Another important question concerns obese individuals who undergo gastric bypass surgery. Their insulin levels fall indicating that insulin secretion is reduced (13), but how much of this is caused by a fall in β-cell mass and how much by inactivation of islets?

Could the presence or absence of activation account for some of the mysteries of islet heterogeneity? For example, in type 2 diabetes the severity of amyloid deposits is quite patchy (14). Perhaps inactive islets are less prone to such deposition. We have a similar question about type 1 diabetes in that some islets are infiltrated with lymphocytes and others are spared (15). Could active islets be more susceptible to autoimmune attack?

This is the very beginning of the sleeping islet story. Let us see where it takes us.

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