Exocrine and Endocrine Interactions in Cystic Fibrosis: A Potential Key to Understanding Insulin Secretion in Health and Disease?

The study of β-cell function in vivo has been hampered by the relative inaccessibility of the pancreas as well as the hybrid exocrine/endocrine nature of the organ. This has limited the ability to correlate structure with function, although some efforts have been made in this regard (1,2). Moreover, there are no tests available that can easily, accurately, and reproducibly measure β-cell secretion in a way that might be clinically relevant or influence therapeutic decisions for individual patients (3). The issue is further compounded by the conflation of β-cell function with β-cell mass, where the former can be taken to represent response to a “physiological” challenge and the latter is represented by the (presumed) maximal response to a “supra-physiological” challenge (4). How these relate to the numbers of functional islets or to islet “health” and integrity remains unknown, despite numerous efforts to image β-cell mass in vivo. Unfortunately in a time when an echocardiogram is routinely used for the assessment of cardiac structure and function, diabetologists are stuck with the equivalent of Laennec’s stethoscope.

The response to a meal is affected by multiple factors (Fig. 1), including gastric accommodation, gastric trituration of complex food, intraluminal digestion, and subsequent absorption (5–8). In addition, the prevailing degree of insulin action will also alter β-cell secretion; indeed for glucose tolerance to be maintained, β-cell function must be able to compensate for impaired insulin action (4). This concept is embodied in the disposition index, which describes the hyperbolic relationship between the two parameters (9) (Fig. 1). Examination of insulin secretion in disease states where these parameters are directly or indirectly affected by the disease process provides a unique opportunity to better understand the interaction of these parameters in modulating insulin secretion.

Cystic fibrosis is one such disease, and hopefully the experiments reported by Sheikh et al. (10) in this issue of Diabetes are the first in a series of studies examining this proposition. Subjects with pancreatic-insufficient cystic fibrosis (PI-CF) were compared with subjects with pancreatic-sufficient cystic fibrosis (PS-CF). Pulmonary function did not differ between groups. Healthy age-, sex-, and weight-matched control subjects were also studied using a glucose-potentiated arginine test, a mixed meal, and 72-h continuous glucose monitoring. All participants met criteria for normal glucose tolerance prior to study.

Sheikh et al. (10) report that arginine-stimulated insulin secretion was greater in PS-CF compared with the other two groups. Conversely, when potentiated by hyperglycemia, arginine-stimulated insulin secretion was lower in PI-CF. C-peptide–based measures of insulin secretion produced similar results, implying that between-group differences were not explained by differences in hepatic insulin extraction. Glucagon responses were also impaired in the PI-CF group.

In response to a mixed meal, glucose was higher and insulin secretion was lower in the PI-CF group. Although insulin secretion did not differ from control subjects in the PS-CF, this group exhibited impaired insulin action measured by the oral minimal model (of note, the M/I ratio did not differ during the hyperglycemic clamp performed as part of arginine stimulation). However, it remains to be ascertained whether insulin secretion in this group was indeed appropriate for the prevailing insulin action via calculation of a disposition index. Unfortunately, the time course of insulin secretion reconstructed by deconvolution in this experiment is dependent on the concentration and time course of plasma glucose. As such, it cannot be used in lieu of a parameter of β-cell responsivity normalized to

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Another interesting finding noted during the mixed meal was the impaired (active) glucagon-like peptide 1 (GLP-1) and (total) gastric inhibitory polypeptide response to meal ingestion in the PI-CF group.

Ultimately, the processes driving the temporal decline in secretory function that lead to diabetes in patients with and without cystic fibrosis are poorly understood. However, there are some important observations arising from the study of islet function that provide context to this series of experiments. Insulin release in response to hyperglycemia is a composite of de novo synthesis, docking, and release of preformed insulin granules assembled and stored during fasting (11). Isolated islets, isolated perfused pancreata, and the in vivo response to (intravenous) glucose is characterized by a biphasic pattern (12). First-phase insulin secretion is thought to represent the release of preformed, stored insulin granules, whereas the second phase represents secretion of newly synthesized insulin (13). Multiple studies demonstrate absent first-phase secretion in people with type 2 diabetes (14).

Does this explain the decreased and delayed response to an oral challenge? What is its significance? Is insulin granule storage truly defective in type 2 diabetes or is it representative of a global synthetic defect? How do these compare with those obtained using arginine with or without glucose potentiation? Intravenous arginine depletes preformed insulin granules (15,16). Subsequent insulin secretion in response to hyperglycemia (if measured at frequent intervals) would be likely to represent the provision of new insulin by de novo synthesis and might provide additional insight into the mechanisms leading to defective insulin secretion in people with type 2 diabetes (or cystic fibrosis).

Orskov et al. (17) demonstrated that intravenous arginine also increases GLP-1 release in the absence of oral stimulation. The significance of this is unknown, and at present, there is little data as to how the GLP-1 response to intravenous arginine changes across glucose tolerance states. Certainly, venous concentrations of GLP-1 do not differ significantly in normal and impaired glucose tolerance or in overt type 2 diabetes and do not correlate with indices of β-cell function (18,19). GLP-1 secretion is affected by luminal nutrient concentrations and gastointestinal motility (20). The significance of the decreased incretin hormone concentrations observed in PI-CF remains unclear at present but may represent enteroendocrine dysfunction unique to cystic fibrosis. One might speculate that in the presence of pancreatic insufficiency, despite pancreatic enzyme replacement, a decrease in the products of intraluminal digestion impairs incretin hormone secretion, which seems to primarily affect postprandial de novo insulin synthesis (21).
Insulin concentrations reflect the net sum of two processes—insulin secretion and hepatic insulin clearance—which may change independently with worsening glucose tolerance (22). Therefore, measurement of insulin secretion is best accomplished from deconvolution of C-peptide concentrations, as was the case in the study by Sheikh et al. (10). This is necessary because the half-life of C-peptide is longer than that of insulin and accumulates in the circulation. Knowledge of its clearance is necessary to calculate insulin secretion (23). However, estimating proinsulin secretion from proinsulin concentrations is problematic as proinsulin has a long half-life in the circulation and the kinetics of its clearance in individuals is not well characterized. A proinsulin–to–C-peptide ratio does not solve this problem, as the half-life of C-peptide differs from that of proinsulin, limiting the usefulness of this parameter (4).

Given this background, we hope that the study by Sheikh et al. (10) spurs further mechanistic studies of diabetes in cystic fibrosis, with a focus on the role of pancreatic exocrine function, intraluminal digestion of nutrients, and enteroendocrine inputs into insulin secretion. This may help develop novel insights into the processes that drive postprandial insulin secretion in health, in cystic fibrosis, and in type 2 diabetes. In that context, the current study is an important first step in this direction.

Funding. A.V. is funded by the National Institutes of Health (DK78646). His studies are performed in the Mayo Clinic General Clinical Research Center (UL1 TR000135).

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

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