β-Cell Glucose Sensitivity Is Linked to Insulin/Glucagon Bihormonal Cells in Nondiabetic Humans

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Context: Insulin resistance impacts virtually all tissues, including pancreatic β cells. Individuals with insulin resistance, but without diabetes, exhibit an increased islet size because of an elevated number of both β and α cells. Neogenesis from duct cells and transdifferentiation of α cells have been postulated to contribute to the β-cell compensatory response to insulin resistance.

Objective: Our objective was to explore parameters that could potentially predict altered islet morphology.

Methods: We investigated 16 nondiabetic subjects by a 2-hour hyperglycemic clamp to evaluate β-cell secretory function. We analyzed pancreas samples obtained during pancreatoduodenectomy in the same patients to examine glucagon and insulin double+ cells to assess islet morphology.

Results: Among all the functional in vivo parameters of insulin secretion that were explored (basal, first phase and total secretion, glucose sensitivity, arginine-stimulated insulin secretion), β-cell glucose sensitivity was unique in exhibiting a significant correlation with both islet size and α-β double+ islet cells.

Conclusions: Our data suggest that poor β-cell glucose sensitivity is linked to islet transdifferentiation, possibly from α cells to β cells, in an attempt to cope with higher demands for insulin secretion. Understanding the mechanism(s) that underlies the adaptive response of the islet cells to insulin resistance is a potential approach to design tools to enhance functional β-cell mass for diabetes therapy. **(*J Clin Endocrinol Metab* 101: 470–475, 2016)**

Type 2 diabetes (T2D) develops when insulin secretion fails to cope with worsening insulin resistance (1). It has also been shown that β-cell function decline is associated with increasing glucose levels (2), even in patients with normal glucose tolerance, and further worsens with the onset of clinically detectable impaired glucose tolerance and progression to T2D (3). Notably, the absence of overt diabetes in individuals with severe insulin resistance suggests the ability of the islet cells to adapt and secrete insulin to maintain glucose homeostasis. Therefore, to explore whether islet cell plasticity is linked to an organism's ability to compensate for insulin resistance, we have recently examined the mechanisms that maintain glucose homeostasis in response to different metabolic demands. Our findings indicate an increased islet size and an elevated number of both β and α cells (resulting in an altered

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Abbreviations: βCGS, β-cell glucose sensitivity; HbA1c, glycated hemoglobin; T2D, type 2 diabetes.

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