COMMENTARY

Does Inhibition of β-Cell Proliferation by Free Fatty Acid in Mice Explain the Progressive Failure of Insulin Secretion in Type 2 Diabetes?

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Large prospective studies have shown that insulin secretion declines over time in patients with type 2 diabetes (1). This makes treatment of these patients a moving target, i.e., a regimen that works today may not work next year. The cause or causes for the progressive decrease in insulin secretion rates over time remains uncertain, but several possibilities have been proposed including amylin accumulation in β-cells (2), glucotoxicity, lipotoxicity, and glucolipotoxicity. The concept that prolonged hyperglycemia results in impaired insulin secretion (i.e., glucotoxicity) was first proposed by Unger and Grundy (3) and is now generally accepted. Lipotoxicity, defined as inhibition of insulin secretion by elevated plasma levels of free fatty acid (FFA), was also first proposed by Unger (4). It is supported by many in vitro studies but has remained controversial mainly because inhibitory effects of chronically elevated FFA levels on insulin secretion have been difficult to demonstrate in subjects with normal islets (rev. in 5). On the other hand, the combination of chronically elevated plasma glucose and FFA levels (glucolipotoxicity) has been demonstrated to inhibit insulin secretion from normal and abnormal β-cells in vivo (5–7) and in vitro (8).

The article by Pascoe et al. (9) supports the glucolipotoxicity hypothesis and may also provide a molecular explanation for it. These authors infused intravenous lipids (Liposyn II) or glucose or both together continuously for 4 days into mice. They found that lipid infusions did not alter basal β-cell proliferation but blocked glucose-stimulated β-cell proliferation without, however, inducing β-cell death. They further showed that incubation of cultured mouse β-cells or INS-1 cells with linoleic acid or palmitic acid inhibited β-cell proliferation and that the inhibition may have been caused by increased expression of the inhibitor of kinase family cell cycle inhibitors p16 and p18.

Can these novel and intriguing observations help us to better understand the reasons responsible for the progressive β-cell failure in many patients with type 2 diabetes and perhaps point to ways to delay and prevent it? To approach this question, we need to first consider the species difference. Mice are not men (or women), especially not with respect to β-cells. Mouse islets are different from human islets. In mouse islets, α-cells are arranged at the

islet periphery surrounding the β-cells, which are clustered in the core. In human islets, α- and β-cells are closely associated with each other and scattered throughout the islets (10). These cytoarchitectural differences are very likely to have functional consequences. In the study by Pascoe et al. (9), there are indeed clues for such differences.

In that study, fatty acids, particularly linoleic and palmitic acids, inhibited glucose stimulation of β-cell proliferation. If similar events were to occur in humans, it would suggest that in patients with type 2 diabetes elevated FFA levels may be the reason why their β-cells are unable to adapt to chronic hyperglycemia and eventually fail. The question, therefore, is what is known about β-cell proliferation, β-cell failure, and FFA in human subjects. It seems reasonably well established that the decrease in insulin secretion in patients with type 2 diabetes reflects a loss of β-cell mass (11–13) and, at least during the initial stages of the disease, also a loss of functional insulin secretory capacity (14). Thus, data from autopsy studies showed that β-cell mass was 50–60% less in obese diabetic compared with equally obese nondiabetic individuals (12,13). β-Cell mass depends on the balance between proliferation, (i.e., of existing β-cell replication plus formation of new β-cells) and β-cell death (apoptosis). In mice, the dominant adaptive mechanism to hyperglycemia appears to be β-cell proliferation (15). On the other hand, the loss of β-cell mass in patients with type 2 diabetes was found to be primarily due to increased apoptosis, whereas β-cell replication was very low and β-cell neoformation, although increased in obesity, was the same in obese diabetic and nondiabetic subjects (13). Thus, the fatty acid–induced inhibition of glucose-initiated β-cell proliferation, demonstrated in the study by Pascoe et al. (9), appears to be more relevant for rodent than human pathophysiology.

The results of the glucose and glucose plus lipid infusions revealed still other differences between mouse and human β-cell responses. For instance, in contrast to human subjects (16), in the study by Pascoe et al. in mice, raising fatty acids did not potentiate hyperglycemia stimulated insulin secretion. Also, the hyperglycemia-induced rise in insulin levels in these mice lasted only ~24 h, after which insulin levels returned to basal. In contrast, in human subjects, a comparable degree of hyperglycemia increased insulin levels and insulin secretion rates, which remained elevated for the duration of the 72-h infusions (17). Interestingly, the rapid (within 24 h) decrease of the elevated insulin levels in mice occurred regardless of whether fatty acid levels were increased or decreased and thus were not likely to be related to any fatty acid–mediated effects on β-cells.

In summary, Pascoe et al. have provided data pointing to a heretofore unrecognized mechanism by which fatty acids can produce β-cell glucolipotoxicity in mice. The

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differences between mouse and human β-cell architecture and adaptive responses to hyperglycemia (outlined above) as well as differences in study design (the mice in the study by Pascoe et al. [9] had free access to chow while being infused with glucose and/or lipid) make it uncertain that these findings in mice are relevant for human β-cell pathophysiology; clearly, however, the new molecular mechanisms discovered by Pascoe et al. need to be further explored.

ACKNOWLEDGMENTS

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