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A NEET Way to Impair Mitochondrial Function in α - and β -Cells

Diabetes 2016;65:1484–1486 | DOI: 10.2337/dbi16-0011



Glucose homeostasis requires a carefully orchestrated balance between the release of insulin and glucagon by β - and α -cells, respectively, in pancreatic islets. During fasting, the rate of insulin secretion falls to slow glucose utilization, whereas that of glucagon secretion rises to promote gluconeogenesis, thereby preventing hypoglycemia. After a mixed meal, glucose stimulates insulin secretion while inhibiting glucagon secretion. This “yin and yang” pattern of β - and α -cell activation and inhibition is very important for the regulation of glucose homeostasis, and dysregulation of pancreatic hormones is a prominent feature of diabetes. It has been appreciated for some time that mitochondrial dysfunction is observed in the β -cells of patients with diabetes (1,2) and that mitochondrial DNA mutations in humans or targeted disruption of mitochondrial genome maintenance in mice are sufficient to drive β -cell dysfunction (3,4). However, the primary mitochondrial defects studied in β -cells to date have generally been severe, and neither the cause nor the consequences of the milder mitochondrial dysfunction observed in the majority of patients with diabetes have been firmly established. Moreover, the consequences of mitochondrial dysfunction in α -cells are relatively unexplored.

In this issue of *Diabetes*, Kusminski et al. (5) introduce tetracycline-inducible expression mitochondrial protein mitoNEET in α - or β -cells as a model of graded mitochondrial dysfunction. MitoNEET (named for its COOH-terminal Asn-Glu-Glu-Thr amino acid sequence) is a mitochondrial outer membrane protein that is oriented toward the cytoplasm and binds iron-sulfur clusters (6,7). Its overexpression in adipocytes suppresses transport of iron into the mitochondrial matrix and consequently reduces respiratory capacity, resulting in elongated, fused, and dysfunctional mitochondria (6). Thus, it was hypothesized that induction of mitoNEET in α - and β -cells using doxycycline (a tetracycline analog) would allow control over both the timing and degree of mitochondrial dysfunction.

Phenotypically, the induction of mitoNEET in β -cells of male (but interestingly, not female) mice resulted in hyperglycemia and glucose intolerance with reduced insulin secretion. This correlated with a decrease in both the size and number of pancreatic islets (Fig. 1). Titrating the induction of mitoNEET to a level where there was no β -cell loss (as judged by circulating insulin concentrations) still led to some degree of glucose intolerance, implying a systemic effect of mild β -cell impairment or perhaps a defect in first-phase insulin secretion that was not detected. When mitoNEET was induced to a degree sufficient to cause β -cell loss, vacuolar structures consistent with autophagosomes were detected, and mitochondria lacking defined cristae were found in large clusters within the cells. Hypothesizing that mitoNEET-induced dysfunction was leading to mitochondrial membrane depolarization and subsequent autophagic degradation (mitophagy), Kusminski et al. (5) next crossed their mice to a strain lacking Parkin, an E3 ubiquitin ligase that is a key player in this process (8). Impressively, the Parkin knockout mice expressing mitoNEET displayed normal insulin secretion, did not accumulate autophagosome-like structures in β -cells, and were partially protected from hyperglycemia and glucose intolerance. This suggests that β -cell loss in response to mitoNEET is indeed secondary to excessive activation of mitophagy through the Parkin-mediated quality control pathway. In an interesting twist, mitoNEET itself is a target of Parkin's ubiquitin ligase activity, although the functional significance of that interaction remains unknown.

Induction of mitoNEET in α -cells led to hypoglycemia during fasting consistent with a defect in glucagon secretion. However, the more prominent effect of this intervention actually appears to be hypersecretion of insulin. The change in β -cell function was somewhat surprising given that past work has focused mainly on communication in the reverse direction from β -cells to α -cells. The

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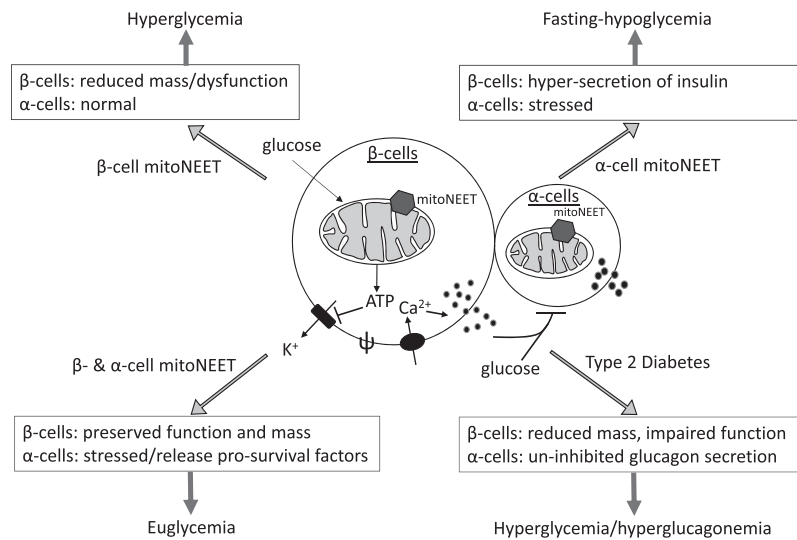


Figure 1—The effect of mitoNEET induction on mass and function of pancreatic islets. The oxidation of glucose in β -cells via mitochondria produces ATP, which closes ATP-dependent potassium channels. This causes β -cell depolarization and calcium influx, which triggers insulin secretion. Factors released from β -cells contribute to glucose-mediated suppression of α -cell function. Induction of mitoNEET in β -cells, α -cells, or both have different impacts on β -cell mass and function, resulting in different in vivo phenotypes that partially—but not completely—resemble the conditions in type 2 diabetes.

architecture of islets in rodents places β -cells in the interior with α -cells at the periphery, and blood flow has been determined to be largely from β -cells to α -cells (9). Consistently, a paracrine mechanism has been proposed involving factors released from β -cells during insulin secretion that control α -cell glucagon release (10). Although complete ablation of α -cells has been reported to expand the β -cell compartment (11), the potential for glucagon or other α -cell-derived factors to regulate insulin secretion is not well studied. In further support of α -cell to β -cell communication in the mitoNEET-expressing mice, Kusminski et al. (5) found that simultaneous induction of mitoNEET in both α - and β -cells rescues β -cell loss, leading them to propose that dysfunctional α -cells secrete a survival factor that can maintain β -cell viability in the face of stress. Transcriptional profiling revealed nerve growth factor α (*Ngfa*) and trefoil factor 2 (*Tff2*) as two candidates that are highly upregulated in mitoNEET-expressing α -cells and known to activate antiapoptotic signaling cascades in β -cells (12,13). However, whether secretion of these factors from α -cells can account for either β -cell survival or hypersecretion of insulin and how they might reach the β -cells remain to be determined.

One important consideration for experiments with β -cell-specific mitoNEET mice is that changes in circulating glucagon do not resemble those observed in type 2 diabetes. Type 2 diabetes is considered a bihormonal disorder characterized by dysfunctional β -cells and hyperfunctional α -cells, with hyperglucagonemia contributing significantly to the hyperglycemia phenotype. As noted by Wollheim and colleagues (10), the normal control of glucagon secretion in islets remains an enigma. It has been proposed that β -cells exert paracrine control of

α -cell glucagon release via inhibitory signals released during glucose stimulation including insulin itself or cosecreted molecules such as Zn^{++} , GABA, and γ -hydroxybutyrate (10,14,15). However, it is not clear whether the release of insulin or its cosecreted granule products provide an adequate explanation. Indeed, it has been emphasized that the glucose concentration for maximal suppression of glucagon release is below the level at which insulin release begins to be activated (16,17). Direct measurement of glucagon secretion from islets isolated from organ donors with type 2 diabetes suggested that they have impaired glucose-mediated glucagon suppression, which may be related to the impaired metabolic control of K_{ATP} channels in α -cells (15,18). In contrast to the hyperglucagonemia in type 2 diabetes, lower-than-normal levels of glucagon were exhibited by mitoNEET-expressing mice during fasting. This discrepancy suggests two possibilities: 1) direct inhibition of glucagon secretion by glucose is impaired in diabetes but normal in mitoNEET mice or 2) factors released from β -cells to inhibit α -cells are impaired by diabetes but not by mitoNEET induction.

Much work remains to be done, but it is already clear that induction of mitoNEET provides a fascinating new tool to probe the interactions between α -cells and β -cells and to examine the consequences of endocrine dysfunction for whole-body metabolism.

Funding. C.L. is supported by National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) grants DK-09-8517 and DK-09-8656. J.A.B. is supported by National Institute on Aging grant AG-04-3483 and NIDDK grant DK-09-8656.

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

