Decreased Insulin Secretion in Type 2 Diabetes: A Problem of Cellular Mass or Function?

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Type 2 diabetes is characterized by diminished or inappropriate secretion of insulin, which could be a defect of either islet cell function or β-cell mass. Quantitation of islet cell populations in postmortem pancreas demonstrates little change of β-cell mass in type 2 diabetes. Reduction of islet cell mass (up to 30%) is associated largely with islet amyloid deposition, and the degree of amyloidosis is independent of the duration of the disease. Insulin secretory capacity is dependent on both function and mass of cells. β-Cell secretion is heterogeneous; increasing glucose concentrations result in recruitment of β-cells into the secretory pool, indicating a large reserve of secretory capacity that can be recruited in insulin resistant conditions. The Starling curve of islet function describes the relationship of insulin secretion to increasing levels of insulin resistance and hyperglycemia in type 2 diabetes. Longitudinal studies in *Macaca mulatta* monkeys show that insulin resistance is accompanied by increased islet mass and onset of diabetes is associated with deposition of amyloid and reduction of β-cells. Increasing the function of unresponsive β-cells rather than the mass of cells may be a more effective therapeutic target for type 2 diabetes. *Diabetes* 50 (Suppl. 1):S169–S171, 2001

The capacity for insulin secretion at diagnosis of type 2 diabetes is largely preserved, but the response to β-cell secretagogues is not equivalent to that seen in nondiabetic subjects (1,2). This could result from quantitative or qualitative changes in pancreatic β-cell mass, possibly in the form of a predetermined susceptibility factor as has been proposed in the Barker-Hales hypothesis, in which a reduction in β-cell mass is the major feature of diabetes-prone, small babies of undernourished mothers (3). Alternatively, the insulin secretory defect could be genetically determined as proposed in Kearns-Sayre syndrome (4), in which there is a decrease in β-cell mass rather than function. Determination of the contribution of a reduction of β-cell secretion is complicated by parallel changes in insulin resistance that accompany onset of type 2 diabetes (5). However, assessment of insulin secretion can be made independently of changes in insulin sensitivity by mathematical modeling (homeostatic model assessment) (6), which indicates that insulin secretion is reduced at the time of diagnosis and further diminishes during the course of the disease (7). The question therefore remains whether there is inadequate cellular capacity to maintain insulin secretion in type 2 diabetes, the reduced insulin secretion results from cellular dysfunction in an appropriate number of β-cells, or a combination of both factors. Furthermore, we need to understand what factors are associated with the progressive decrease in islet function during the disease and how this can be ameliorated by appropriate therapy.

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QUANTITATIVE CHANGES IN ISLET CELL POPULATIONS IN TYPE 2 DIABETES

In the normal islet, β-cells occupy 60–80% of the islet volume, non–β-cells and capillaries providing the remainder. Islets form ~3–5% of the pancreatic mass (8,9) and are distributed in an apparently random manner when viewed in tissue sections. However, the location of islets is related to their ontogeny; the relatively large islets in mice are clearly situated adjacent to pancreatic ducts from which they form in fetal development by differentiation from ductal stem cells (10,11). Islet development commences at 10 weeks' gestation in humans, and histological and morphometric analyses suggest that neogenesis continues into childhood, with relatively large numbers of extra-islet β-cells forming from ductular stem cells (12,13). However, because endocrine cells are rare in the ductal epithelium of adults, it has been assumed that islet mass is predetermined during early years of life and is relatively static in adult nondiabetic humans. No evidence has been found for replication of endocrine cells within islets, which are therefore, like neurones, considered to be postmitotic. However, in acute and chronic pancreatitis and in some adenocarcinomas, proliferation of duct epithelium is associated with endocrine cell neogenesis (14). In rodents, islet cells associated with ducts are more frequent, especially after partial pancreatectomy associated with hyperglycemia (15).

Quantitative estimates of islet and β-cell populations in type 2 diabetes have been made in postmortem pancreas and compared with those of nondiabetic age-matched subjects (8,9,16). The results show that the β-cell population in diabetes is either similar or reduced by up to 30% when accompanied by deposition of islet amyloid. A small, but significant, increase in the number of α-cells has also been detected (8,9). Neogenesis of islet cells from duct cells can be identified by immunolabeling for the ductal cell epithelium protein, cytokeratin19, and islet peptides (17). This method has demonstrated that there are

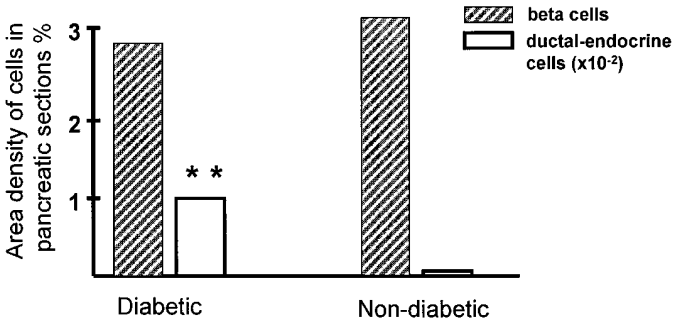

FIG. 1. Islet and ductular β-cells in pancreatic sections of type 2 diabetic and nondiabetic subjects. Postmortem pancreatic tissue from nine type 2 diabetic and nine nondiabetic subjects of similar ages was labeled by immunohistochemistry for insulin and for the duct marker cytokeratin19. Areas of labeled cells within the islet and associated with ducts were determined by semiquantitative morphometry (IBAS, Kontron, Germany), and the mean area density was determined. Although there was no significant difference in the islet β-cell area density/exocrine tissue, the area density of ductular β-cells was significantly increased (1×10^{-2} in the diabetic subjects and 0.06×10^{-2} in the nondiabetic subjects), $P = 0.002$.

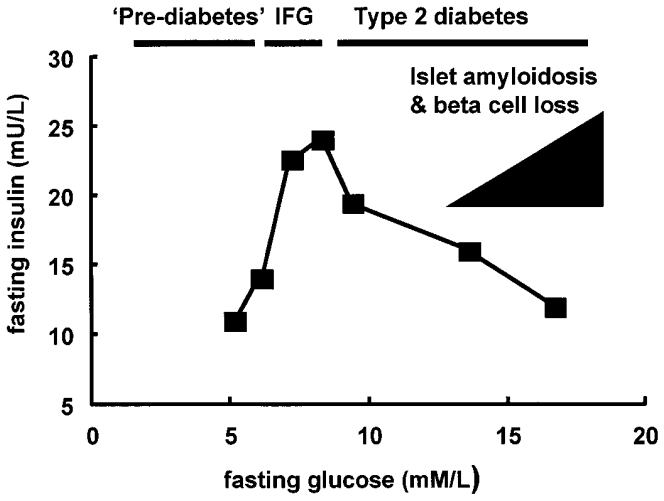

FIG. 2. Cross-sectional data adapted from de Fronzo et al. (23). demonstrating the Starling curve of β-cell function at different stages of type 2 diabetes. Fasting insulin increases with increased insulin resistance. Once the peak of insulin secretion has been achieved, progressive decline in insulin secretory capacity is unlikely to be reversed. This leads to eventual β-cell failure, which may be accompanied by decreased β-cell mass and islet amyloidosis.

many newly forming ductular β-cells in human fetal and neonatal pancreas, whereas the numbers decrease in adult pancreas (12,17). Studies in postmortem pancreas have shown a larger number of ductal cells that are insulin immunoreactive in type 2 diabetes compared with nondiabetic specimens (Fig. 1). This suggests that β-cell neogenesis is increased in type 2 diabetes. This increase could be caused by subclinical chronic pancreatitis, which is evident from the degree of fibrosis in these specimens (8), or by hyperglycemia. It is unclear if these newly formed islets enter into the secretory pool.

The small changes in β-cell population in type 2 diabetes (0–30%) are independent of the duration of diabetes (2–40 years) (8,9). It therefore seems likely that a large reduction in β-cell mass is not the precipitating factor for onset of diabetes. A 95% partial pancreatectomy is required to induce hyperglycemia in rodents (18), but a 50% reduction in β-cell mass induced by streptozotocin results in hyperglycemia in baboons (19). It is thus possible that in primates (including humans) physiological insulin secretion requires a larger population of β-cells than in rodents and that relatively small changes in the β-cell population can affect glucose homeostasis.

β-CELL DYSFUNCTION RATHER THAN β-CELL LOSS

There is considerable evidence that the degree of insulin secretion, particularly in response to glucose, is not determined entirely by the absolute size of the β-cell population. Hyperinsulinemia associated with increased insulin resistance is thought to reflect increased secretory capacity from the same population of β-cells. The heterogeneity of secretory responses of β-cells is well recognized (20–22). In vitro, low concentrations of glucose (6–8 mmol/l) induce increased secretion from a small population of isolated β-cells, and increasing glucose concentration recruits more cells into the secretory pool and also augments secretion from the initially responsive cells (20,21). The reason for this differential sensitivity to glucose is unclear. It is possible that in vivo <50% of the total β-cell population are responsive to changes in glucose at any one time and that this redundancy creates a large reserve of secretory capacity that can be mobilized in insulin-resistant conditions. The Starling curve of β-cell function describes how this process can progress to a pathological condition in type 2 diabetes but does not implicate anatomical gain or loss of β-cells until late in the disease process (23) (Fig. 2). The point at which the secretory capacity no longer remains flexible results in progression to diabetes but without a substantial change in β-cell mass, since no dramatic changes in β-cell number are seen in pancreatic tissue from type 2 diabetic subjects. However, in type 2 diabetes, it is possible that the initial β-cell mass is not adequate to compensate for the required changes in insulin secretory capacity. Conditions shown to reduce islet development include mitochondrial mutations in humans (4) and environmental factors such as poor nutrition in utero in animal models (24).

β-CELL MASS, ISLET AMYLOID, AND DIABETES IN HUMANS AND ANIMAL MODELS OF DIABETES

Deposition of amyloid formed from islet amyloid polypeptide is a characteristic feature of islets in type 2 diabetes. Amyloid deposits have been identified in at least one islet in histological sections of postmortem pancreas in up to 96% of patients with type 2 diabetes (25). Islet amyloid deposition is a progressive process, and the degree of islet amyloidosis is associated with more severe deterioration in islet function, as shown by the requirement for insulin therapy in humans (26,27). In monkeys, deposition of amyloid fibrils results in replacement of β-cells (Fig. 3) (28). *Macaca mulatta* monkeys fed ad libitum develop a syndrome of diabetes associated with obesity, insulin resistance, and β-cell failure as seen in humans (29). Fasting plasma insulin was determined from 6–8 monkeys at different stages of the diabetic syndrome; this was compared with the density of β-cells and islet amyloid in postmortem specimens of pancreas taken from 25 animals at different stages (29). The relationship between the secretory activity and the pancreatic cellular density was determined by comparing the longitudinal and cross-sectional data (Fig. 3). Increased insulin secretion in

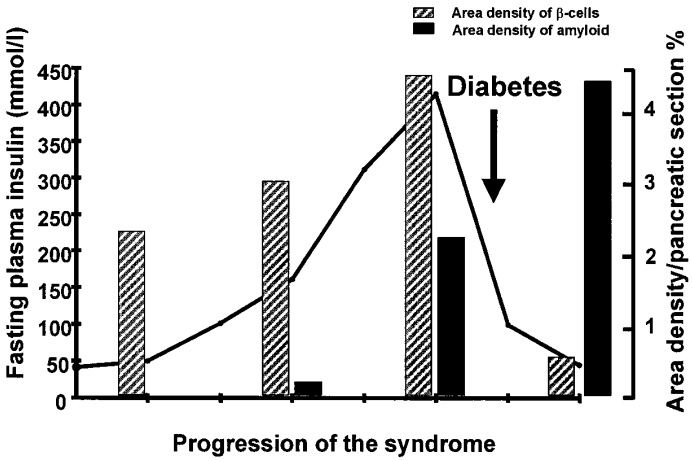

FIG. 3. Insulin secretion and islet changes in the diabetic syndrome of *M. mulatta*. Fasting insulin was determined in 6–8 monkeys at different points in the stages of the syndrome (continuous line), and the area density of β-cells and amyloid were determined from postmortem material of 25 other animals. Increased obesity and insulin resistance was associated with increased fasting insulin concentrations (but normoglycemia) and an increase in the islet size and pancreatic area density of β-cells. However, a point was reached at which fasting insulin was reduced, and this was accompanied by diabetes, a fall in the proportion of β-cells, and a rise in the degree of islet amyloidosis. In this species, unlike humans, substantial amounts of islet amyloid were present before the onset of hyperglycemia. Data interpreted and extended from published data (28,29).

obese, insulin-resistant animals was accompanied by increased islet size and pancreatic proportion of β-cells (Fig. 3). This stage of the syndrome was followed by decreased insulin secretion and diminished islet and β-cell mass, development of islet amyloid, and diabetes; the degree of islet amyloidosis determined by morphometric assessment of histological sections was proportional to the decreased islet mass (29). Although in some animal models of diabetes islet amyloid forms before the onset of hyperglycemia (30,31), in humans, islet amyloidosis is a candidate pathology for the severe deterioration of insulin secretory capacity during the final stages of the syndrome.

The factors that determine the development and sustainability of appropriate β-cell mass for glucose homeostasis in humans may be less flexible and may depend on a higher degree of redundancy than in rodents. Increasing the function rather than the mass of β-cells could be a more effective treatment of type 2 diabetes. The final demise of insulin secretory capacity that is linked to amyloid-induced cytotoxicity is a target for therapies directed toward preservation of islet function in type 2 diabetes.

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