β-Cell Dysfunction and Failure in Type 2 Diabetes
Potential Mechanisms

Daniel Porte, Jr., and Steven E. Kahn

Type 2 diabetes is characterized by a progressive loss of β-cell function throughout the course of the disease. The pattern of loss is an initial defect in early or first-phase insulin secretion, followed by a decreasing maximal capacity of glucose to potentiate all nonglucose signals. Last, a defective steady-state and basal insulin secretion develops, leading to complete β-cell failure requiring insulin treatment. This functional loss exceeds the expected impact of a 20–50% loss of β-cells reported at autopsy, which has been associated with amyloid deposits. This review summarizes the nature of the amyloid deposition process and its association with disproportionate hyperproinsulinemia. It reviews recent studies in IAPP (islet-amyloid polypeptide, or amylin) transgenic mice developing islet amyloid deposits and hyperglycemia to suggest that the process of amyloid fibril formation impairs function early and leads to β-cell failure and eventual death. Based on the known association of amyloid deposits and relative hyperproinsulinemia, it is hypothesized that fibril formation begins during impaired glucose tolerance after other factors cause the initial defects in early insulin secretion and insulin action. Thus, the process that leads to β-cell loss is implicated in the deposition of amyloid and the late unrelenting progressive hyperglycemia now found in all patients despite current therapies. *Diabetes* 50 (Suppl. 1):S160–S163, 2001

β-CELL DYSFUNCTION

β-Cell dysfunction in type 2 diabetes is characterized by a gradual progressive decline from near-absent first-phase glucose-induced insulin secretion to impaired second-phase insulin secretion, glucose potentiation, and disproportionate hyperproinsulinemia, with impaired basal or steady-state insulin secretion (1,2). Patients with clinical disease and fasting hyperglycemia are at the end stage of this process and demonstrate all of these features. The remarkable finding is that hyperglycemia compensates for the impaired glucose potentiation and second-phase defect so that, at the intermediate stages of final β-cell failure (fasting plasma glucose <200 mg/dl), nonglucose secretogogues are able to produce an insulin response that is absolutely normal in both magnitude and timing (3,4). This response includes such diverse signals as glucagon-like peptide 1, secretin, the β-adrenergic agonist isoproterenol, tolbutamide, arginine, and other amino acids. In a small number of studies we performed some time ago, the impact of glycemic potentiation was very similar for all of these stimuli. Therefore, we have concluded that because we have found no data indicating otherwise, the defect is related to an islet mechanism that is directly related to the unique way in which glucose regulates insulin secretion.

β-CELL MASS

We have considered the possibility that a reduction in islet mass could by itself produce such a finding. However, in our experience, the destruction of a part of the pancreas produces a functional change that is different. Thus, when the potentiation function of the islet is tested throughout the glucose dose response (100–600 mg/dl), there is normally a maximum at ~450 mg/dl, which is reduced in type 2 diabetes, and a one-half maximum that can be calculated to be between 150 and 200 mg/dl, which is unchanged in type 2 diabetes (5). In contrast, when we studied dogs with a 65% partial pancreatectomy, we observed a 75% reduction in the maximum response, but there was a compensating reduction in the one-half maximum response level (i.e., the residual pancreatic β-cells became more sensitive to glucose) (6). For this reason, there was no clinical or fasting hyperglycemia, and despite the major β-cell loss, first-phase glucose-induced insulin secretion was not significantly reduced. A similar pattern can be seen in prediabetic HLA-identical siblings of type 1 diabetic patients, implying that residual β-cells, though still functioning "normally," attempt to compensate for their deficient mass by increasing their sensitivity to glucose (7). We would suggest that they are compensating for their numerical loss and are near their maximal output per cell, so that the reduced number of β-cells are sufficient to prevent fasting hyperglycemia. Another animal model for β-cell loss is the streptozotocin-treated baboon, which demonstrates a similar pattern of functional change (8).

From these data, a significant loss of β-cells does not seem likely at the early phases of clinical hyperglycemia in type 2 diabetes. This conclusion is supported by autopsy studies suggesting that at death perhaps ≤20–50% of the β-cells have been lost after many years of disease (9–11). Nevertheless, there is strong pathological evidence of some β-cell depletion in autopsied series, and the question concerns the mechanism

From the University of California and Veterans Affairs San Diego Health Care System (D.P.), San Diego, California; and the University of Washington and Veterans Affairs Puget Sound Health Care System (S.E.K.), Seattle, Washington.

Address correspondence and reprint requests to Daniel Porte, Jr., MD, VA San Diego Health Care System (111G), San Diego, CA 92161. E-mail: dporte@ucsd.edu.

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hIAPP, human islet amyloid polypeptide; IAPP, islet-amyloid polypeptide; IGT, impaired glucose tolerance.

for this loss and if it in any way relates to the functional changes that are seen early on.

The primary pancreatic pathology that has been reported is a lack of inflammation, relatively normal-appearing α- and δ-cells, and deposits of amyloid replacing islet β-cells, which in morphology appear otherwise normal. However, whereas the remaining β-cells stain for insulin, they stain relatively poorly for islet-amyloid polypeptide (IAPP) or amylin, the other β-cell peptide that is the major constituent of the accompanying amyloid (12). The magnitude of the replacement of β-cells by amyloid deposits during life is unknown, as are its onset and rate of development; however, in one series of patients with type 2 diabetes, some degree of islet amyloid deposit was present in 90% of the population at autopsy (13). When β-cells are quantified, the estimated magnitude has been a 20–50% loss compared with control subjects. Based on our pancreatectomy and streptozotocin experience, if this loss were the only abnormality, we would not expect clinical hyperglycemia. Furthermore, because the diabetic patients chosen were usually obese, we would expect the absolute number of islets to be approximately the same as in a lean control group. Therefore, even though there may be some relative reduction in β-cell mass in type 2 diabetic patients compared with obese control subjects in association with amyloid replacement, the reduction is modest and no major clinical hyperglycemia would be expected from the mass loss alone.

PANCREATIC ISLET AMYLOID

To assess the potential role of the amyloidogenic process in the diabetic syndrome per se, the human cDNA for IAPP has been expressed under the control of the rat insulin promoter to generate transgenic mice in a number of laboratories. Initial studies failed to find either defects in carbohydrate metabolism or development of classical pancreatic amyloid deposits (14–18). However, in later studies summarized in a recent review (19), Verchere et al. (20) and other groups (21,22) found conditions under which islet amyloid can be induced to develop in association with hyperglycemia. The major precipitating factor in the early Seattle studies was a high-fat diet (20). This treatment of the strain led to significant obesity (doubling in weight), and for the first time, the transgenic males showed pancreatic islet amyloid deposits and an increased incidence of hyperglycemia when compared with controls. Of interest was the finding that a significant number of nonhyperglycemic transgenic males also demonstrated amyloid deposits, though with less overall frequency. Females showed similar findings, but both hyperglycemia and amyloid deposits were also far less frequent. Nevertheless, it is important to point out, again, that the quantitative assessment of the volume of amyloid deposits and β-cell replacement seemed to be insufficient to explain hyperglycemia of the magnitude found in many of the animals, suggesting that the amyloidogenic process may impair function before cell death and replacement by amyloid. Such a possibility has been suggested by in vitro studies demonstrating a toxic cellular effect of spontaneously formed amyloid precursor human fibrils, which were made by simply dissolving large quantities of peptide in vitro and then exposing islets or neurons to the fibrils in culture (23).

Most recently amyloid deposits were found in human islet amyloid polypeptide (hIAPP) transgenic mice that had been crossed with *ob*/*ob* obese mice in one study (21) and with obese A^{vy}/a mice in another (22). In both cases these mutant mice that developed diabetes spontaneously were found to have their diabetes exacerbated with higher glucose and lower insulin levels; and in both cases, particularly in males, amyloid deposits were seen. In those studies, there was a clear dependence of both amyloid deposits and hyperglycemia on the expression efficiency of the hIAPP transgene that varied with the founder used and whether the cross was heterozygous or homozygous for the transgene. Such apparent dependence on hIAPP expression probably explains the lack of amyloid deposits in the previously reported hIAPP crosses with *ob*/*ob*, *db*/*db*, or the gold thioglucose obese mice described above. In previous studies, the transgenic founder mice were relatively low in expression. However, in the Seattle studies, a high-fat diet was more effective than homozygosity or nicotinic acid–induced insulin resistance in leading to amyloid deposit formation and hyperglycemia, despite lower circulating and pancreatic hIAPP levels (20), indicating that factors relating to the high-fat diet other than increased hIAPP expression are important. These factors may well be β-cell dysfunction induced by a high-fat diet, as has been demonstrated in susceptible rodents (24).

HYPERPROINSULINEMIA

In an attempt to relate these data to patients with type 2 diabetes, we have called attention to the only other syndrome to develop clear-cut islet amyloid deposits: islet cell tumors secreting both insulin and insulin precursors (25). Such tumors also secrete IAPP, but the patients are hypoglycemic from the associated hyperinsulinemia. At surgery or autopsy, a high number of pancreatic amyloid deposits have been reported in the tumors. These tumors store insulin poorly and secrete a considerable portion of newly synthesized proinsulin directly by a constitutive mechanism that does not contain the processing enzymes PC-1/3 and PC-2 (26). Thus, patients with tumors are characterized by relative hyperproinsulinemia and pancreatic islet amyloid polypeptide deposits. Patients with type 2 diabetes also demonstrate disproportionate levels of circulating proinsulin and its processing intermediate des-31,32 proinsulin (2). These levels are proportional to the degree of hyperglycemia and inversely related to the functional measure we have deemed the maximum capacity to secrete insulin (27). Based on the findings of amyloid and disproportionate hyperproinsulinemia in these two patient populations, we have postulated that disproportionate hyperproinsulinemia is a marker for the presence of amyloid or amyloid fibrils in both syndromes (25). If this is true, there would be concordance between the onset of clinical hyperglycemia and the onset or early stages of amyloid deposit formation. Furthermore, progression of amyloidosis would be marked by progression of hyperproinsulinemia.

CLINICAL IMPLICATIONS

Data from the landmark U.K. Prospective Diabetes Study indicate that despite treatment with sulfonylureas, insulin, or metformin, hyperglycemia continues to worsen (28) and there is a decline in β-cell function, as calculated according to the homeostasis model assessment (29). Of particular interest is the observation made by several groups that sulfonylurea treatment, though effective at reducing blood glu-

cose levels, does not reverse the relative hyperproinsulinemia, which is consistent with continued progression of the underlying process (30–32).

As for the onset of the amyloidogenic process, some data suggest that this may be an early occurrence. First, relative hyperproinsulinemia has been shown in Japanese-Americans to predict progression from impaired glucose tolerance (IGT) to type 2 diabetes when evaluated retrospectively over a period of 5 years (33). Second, longitudinal studies of *Macaca nigra* who developed spontaneous diabetes in association with pancreatic islet amyloid showed that deposits were present at pancreatic biopsy in the IGT stage, which progressed in severity as metabolism worsened to fasting hyperglycemia (34). Third, whereas all the hyperglycemic hIAPP transgenic mice that were studied by Verchere et al. (20) have amyloid deposits, some normoglycemic animals also have amyloid deposits, though less than that of the hyperglycemic mice. This observation is compatible with the idea that amyloid deposition precedes hyperglycemia, thus suggesting a pathogenic role.

SUMMARY

There is a well-documented loss of pancreatic β-cell mass in type 2 diabetes that almost certainly contributes to the degree of hyperglycemia. This loss is best explained by the simultaneous deposition of amyloid, a product of hIAPP normally produced in the β-cell and secreted along with insulin. The mechanisms for this deposition are not well understood but are under active investigation. It seems reasonable to hypothesize that the process leading to amyloid deposits is responsible for the progressive β-cell failure seen in all treated type 2 diabetic patients. However, it is important to point out that the loss of β-cell function is disproportionately more important than the degree of β-cell loss. It is likely that fibril formation inhibits function early, before amyloid deposits develop; however, independent mechanisms may induce β-cell dysfunction before the development of clinical hyperglycemia. One example is the –30 G→A glucokinase polymorphism we have associated with defective early insulin release and increased risk of IGT in Japanese-Americans (35).

The development of methods to assess pancreatic amyloid deposits in vivo in humans is sorely needed. The possibility of reducing the progressive deterioration of β-cell function that leads to amyloid deposition and β-cell failure after diagnosis is appealing. Studies to impair such fibril formation offer the possibility of developing preventive means for the relentless downhill course of the disease, which is one of our most important clinical problems in type 2 diabetes management at this time.

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