Perspectives in Diabetes

Type II Diabetes, Glucose "Non-Sense," and Islet Desensitization

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A universal finding in hyperglycemic patients with type II (non-insulin-dependent) diabetes mellitus is that all share a common defect in glucose recognition resulting in abnormal insulin secretion by pancreatic islet β-cells. This defect is *1*) specific for glucose signals rather than global, *2*) related to chronic hyperglycemia, and *3*) partially reversible after brief treatment with insulin to induce normoglycemia and through use of other pharmacological agents without normalizing glucose levels. My perspective is that an essential component of this defect is secondary and may represent a state of homologous desensitization of the β-cell secretory apparatus to glucose. Elucidation of the biochemical mechanism(s) of defective recognition of glucose signals by β-cells—or glucose "non-sense"—in these patients will provide key insights into the pathogenesis of type II diabetes mellitus. *Diabetes* 38:1501–1505, 1989

Scientists seem to be irresistibly drawn to reductionistic explanations for biological events. At least as far back as Descartes's seating of the soul specifically in the pineal gland, scientific thinkers have sought definitive and exclusive explanations for natural and unnatural phenomena. Descartes (1) reported

> . . .it seems to me quite clear, after carefully examining the matter, that the part of the body where the soul operates most directly is not the heart, nor is it the entire brain, but only the innermost portion of the brain—a tiny gland situated in the very middle of it, and suspended above the duct through which the animal spirits in the forward passages can communicate with those in the rear ones.

If scientists share one nearly fatal flaw, it is our drive to find ultimate and singular causality. That the crossroads of science are littered with rejected hypotheses and single-cause explanations in no way deters us from reductionism. We continue to concoct "definitive" experiments and then, when the results of our individual and highly restricted experiments yield conflicting conclusions, we collide with one another and argue with great conviction. The old chestnut about blind men and elephants inescapably leaps to mind.

Currently, there are fairly intense pressures to choose among reductionistic explanations for the pathogenesis of diabetes mellitus, including single genetic defects, fundamental metabolic abnormalities in specific tissues, and key destructive cytokines. More holistic investigators emphasize the need to consider diabetes as a multifaceted disease caused by a convergence of diverse pathogenic forces. Although I favor the latter approach, in this perspective, I avoid formulating an "ultimate" explanation for the pathogenesis of diabetes. Rather, I address the thesis that once hyperglycemia, due to whatever cause, is manifest, defective glucose recognition is a specific and at least partially secondary abnormality shared by all type II (non-insulin-dependent) but not type I (insulin-dependent) diabetic patients. I suggest that abnormal β-cell function attributed to defects in glucoreceptors, glucose recognition, or glucose sensing stems at least in part from homologous desensitization of the β-cell secretory apparatus to glucose in the conventional pharmacological sense and that this is an integral part of the metabolic abnormalities observed in patients with type II diabetes mellitus. For brevity, I limit my defense of this thesis to considerations of pancreatic islet function and dwell primarily on experiments in human subjects. However, in addition to the cited studies, there are important reports and unpublished observations bearing on this topic that have used biochemical approaches to study the islet or have used nonislet tissues. The long-term research begun by Mat-

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schinsky and Ellerman (2) is particularly relevant because it suggests glucokinase may serve as an intraislet glucose sensor—a concept that could prove very helpful in discovering mechanistic explanations for defective glucose recognition in diabetes.

DEFECTIVE FIRST-PHASE INSULIN RESPONSE AS SPECIFIC MARKER FOR TYPE II DIABETES

Glucose perifusion experiments in vitro and intravenous glucose stimulation in vivo led to definition of separable phases of insulin secretion (3–5). It was soon recognized that the first-phase but not the second-phase response to glucose is completely absent in hyperglycemic type II diabetic patients (6). The measurement of first-phase response is a valuable tool because it provides a metabolic marker that is either absent or present in contrast to less definitive tests, e.g., the insulin response to oral glucose ingestion, which is present to variable degrees despite hyperglycemia. Brunzell et al. (6) clearly established that a narrow threshold of glycemia exists beyond which intravenous glucose fails to stimulate first-phase insulin responses. They demonstrated that subjects with fasting plasma glucose levels between 79 and 114 mg/dl have intact first-phase responses but that diabetic patients with fasting glucose levels ≥115 mg/dl do not.

Robertson and Porte (7) first reported that hyperglycemic type II diabetic patients who have no first-phase responses to glucose do have first-phase responses to isoproterenol, a β-adrenergic agonist, indicating that these patients have the intracellular processes required for first-phase hormone secretion and that the β-cell defect lies in the recognition of glucose signals specifically. Further evidence for separate pathways for glucose and β-adrenergic signals to the islet was obtained from experiments in healthy subjects in whom propranolol infusions, at rates not affecting glucose stimulation of first-phase secretion, completely obliterated isoproterenol-induced secretion (7). Other investigators published similar findings with various agonists, e.g., secretin, arginine, and glucagon, all of which stimulate first-phase insulin release in type II diabetic patients who have no first-phase response to glucose (8–10). Later, based on glucose-potentiation studies, it was appreciated that the magnitude of the first-phase insulin response to nonglucose secretagogues may frequently be less than normal (11), suggesting refractoriness of β-cells to the potentiating effects of glucose and/or to defective intrinsic responsiveness of β-cells to nonglucose secretagogues. However, more important, first-phase insulin responds at least qualitatively to nonglucose signals when responses to glucose are entirely absent. Hence, there is considerable support from human studies for the concept of defective glucose recognition as a specific abnormal entity in type II diabetic patients.

It is almost impossible to determine whether glucose-specific defects in β-cell function, as found in type II diabetes, occur in established type I diabetes because insulin secretion in the latter is completely absent due to β-cell death. The absence of glucose-induced first-phase insulin responses in islet cell antibody–positive but normoglycemic patients who are destined to eventually develop type I diabetes is of interest because they retain first-phase responses to glucagon (12). However, these findings beg the question of whether glucose desensitization of the islet is responsible for defective responses to glucose because the patients are not yet hyperglycemic. One can turn to the α-cell and glucagon secretion in type I patients to address this issue. Glucagon responses to insulin-induced hypoglycemia are frequently diminished or absent in type I diabetic patients. However, Gerich et al. (13) observed that type I diabetic patients with virtually absent glucagon responses to hypoglycemia have normal responses to intravenous arginine. In a sense, this represents a glucose-specific defect, because the signal for glucagon release that the α-cell fails to recognize is a change in glucose level (a decrease, in this case), and yet the response to a nonglucose signal (arginine) is normal.

Catecholamine responsivity during insulin-induced hypoglycemia also supports the concept of selectivity in abnormal glucose sensing. Many type I diabetic patients have diminished or absent epinephrine responses to hypoglycemia (14). However, type I diabetic patients who have absent catecholamine responses to hypoglycemia have normal catecholamine responses to exercise (15). This is further evidence that hormonal systems in type I diabetic patients can be at least qualitatively normal in their responsiveness to nonglucose signals while failing to recognize changes in circulating glucose levels. However, these findings do not directly address whether hyperglycemia causes these selective defects. Because many hyperglycemic type I diabetic patients do not have abnormal glucagon and catecholamine responses to hypoglycemia and because intensive glucose control does not restore the abnormal responses, hyperglycemia probably does not cause these defects. Although Giaccari et al. (16) argue that chronic hyperglycemia in rodents may cause abnormal glucagon responses to hypoglycemia, some clinicians attribute the abnormal α-cell responses in type I diabetic patients to autonomic neuropathy.

IMPACT OF CHRONIC HYPERGLYCEMIA ON β-CELL FUNCTION

Great importance has been ascribed to controlling hyperglycemia because of its putative contribution to the development of complications involving kidney, nerve, eye, and cardiovascular tissue. Concern has also been expressed that continuously elevated glucose levels may have deleterious effects on pancreatic β-cell function. Bonner-Weir et al. (17) reported that 90% pancreatectomy in rats led to defective insulin responses to glucose but not to arginine when insulin secretion was expressed as a function of β-cell mass. The authors suggested that the amount of hyperglycemia induced by the operation led to chronic stimulation of reduced β-cell mass, which led to selective loss of glucose-induced insulin secretion. This conclusion was reinforced by Leahy et al. (18) and Rossetti et al. (19), who reported data suggesting that chronic postpancreatectomy exposure of residual β-cells to higher than normal glucose concentrations causes insulin secretory defects. Imamura et al. (20) also observed adverse effects of hyperglycemia on residual pancreatic function after pancreatectomy. On the other hand, Ward et al. (21) reported defective arginine-induced insulin secretion 6 wk after partial pancreatectomy when glucose-induced insulin secretion remained normal; however, the animals were not hyperglycemic postoperatively. The results of Bonner-Weir et al. and Ward et al. are

not necessarily in conflict because their experimental models differed in many important aspects. However, they both demonstrated agonist-specific defects in insulin secretion as a consequence of impaired total islet function, which reinforces one of the major contentions of this perspective; i.e., defects in insulin secretion that develop during the evolution of non–type I diabetes mellitus are agonist specific rather than global.

Experiments in humans supporting the possibility of adverse effects of chronic hyperglycemia on islet function include those in which glucose-stimulated insulin secretion in diabetic patients improved after fasting glucose levels had been lowered to normal levels. For example, Turner et al. (22) demonstrated in a small group of type II diabetic patients that lowering mean fasting glucose levels from 7.3 to 4.1 mM by infusing insulin improved glucose-induced first-phase insulin responses by ~2.5-fold. Vague and Moulin (23) conducted similar experiments in hyperglycemic type II diabetic patients with essentially absent first-phase insulin responses to glucose and, after normalizing fasting glucose levels, demonstrated partial restoration of first-phase responses (~2.5-fold over basal insulin levels). First-phase responses to tolbutamide were present before normalization of glucose levels and were not increased by the experiment (23).

Critics of experiments such as these point out that restoration of glucose-induced first-phase insulin secretion is never complete and that results of at least one study failed to find improved first-phase responses after lowering glucose levels with exogenous insulin (24). However, in the study by Garvey et al. (24), the patients' mean fasting glucose levels were lowered to only ~150 mg/dl, a level at which restoration of first-phase responses could not reasonably be expected. More important, whether first-phase response is restored to a completely normal or subnormal level is reminiscent of semantic arguments about whether a glass of water is half empty or half full. The point is that lowering fasting glucose levels briefly into the normal range enables diabetic patients to have an easily measurable first-phase response to intravenous glucose, even though they had absolutely no response previously.

SEARCHING FOR MECHANISMS OF GLUCOSE DESENSITIZATION

The theme emerging from these experiments that I find most fascinating is that the improvement in first-phase insulin secretion in type II diabetic patients that accompanies the lowering of glucose levels into the normal range is specific for glucose signals. In some studies, other agonists were also given, and in no case were improved responses to nonglucose secretagogues observed. This fits nicely with the concept that diabetic patients have recognition defects that are glucose specific rather than global. The situation is similar to homologous desensitization, in which excessive stimulation of a cell by a given agonist leads to downregulation of the cell's responsivity to that agonist but not to others. Karam et al. (25) reported an example of this phenomenon in studies demonstrating desensitization of β-cells to sulfonylureas but not glucagon after treatment with tolazamide. This explanation might also apply to diminished glucose potentiation of nonglucose agonists (11), because it is the glucose signal that serves as the potentiator. If this line of reasoning is accepted for patients with type II diabetes, the operative mechanisms in glucose desensitization of the β-cell secretory apparatus may be considered. In addition to the possibility that desensitization to glucose might be caused directly by glucose or its metabolites, as recently discussed by Grodsky (26), does information from in vivo studies suggest that other substances may be playing a role?

At least three pharmacological maneuvers other than insulin infusion to induce normoglycemia in type II diabetic patients have been reported to result in partial restoration of first-phase glucose-induced insulin secretion. Use has been made of adrenergic antagonists to prevent α-adrenergic input by islet innervation (27,28), naloxone to antagonize endogenous opioid action (29), and nonsteroidal anti-inflammatory drugs to inhibit islet prostaglandin E_2 synthesis (PGE_2; 30–32). After a brief period of treatment (only 1 h in most instances) with these agents, type II diabetic patients with absent first-phase insulin responses to glucose were able to secrete insulin within the normal timing constraints for the first phase. These findings raise the question whether endogenous biogenic amines, opioids, or PGE_2 is operative in

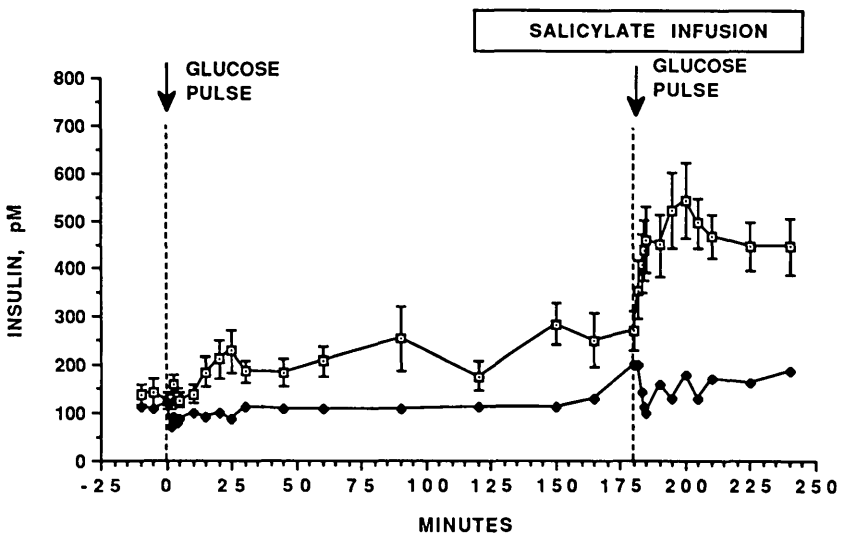

FIG. 1. Restorative effects of sodium salicylate on β-cell function in type II (non-insulin-dependent) but not type I (insulin-dependent) diabetes mellitus. Insulin responses to intravenous glucose (20-g) pulses before and 1 h after onset of sodium salicylate infusion (40 mg/min i.v.) are shown. Type II diabetic patients (□; n = 6; fasting glucose 8.58 ± 2.09 mM, mean ± SD) had no first-phase insulin response before but did during salicylate infusion. Second-phase responses were also markedly improved. In contrast, 16-yr-old type I diabetic patient (♦) early in disease, who was hyperglycemic (fasting glucose 9.35 mM) but not yet treated with exogenous insulin, failed to demonstrate improvement during salicylate infusion.

glucose desensitization of the islet. Because the three unrelated therapeutic approaches are effective despite the presence of hyperglycemia, a mechanism other than hyperglycemia per se may be involved. Without excluding the other two groups, I favor PGE_2 for reasons that have recently been reviewed (33,34). Briefly, glucose stimulates PGE_2 synthesis from β-cells (33), and β-cells have specific high-affinity receptors for PGE_2 whose binding constants are identical with the inhibitory constants for the effects of PGE_2 on adenylate cyclase activity and glucose-induced first-phase insulin secretion (35,36). Both of the events are pertussis toxin sensitive and therefore presumably involve the inhibitory G protein coupled to adenylate cyclase (35,36). Therefore, chronic hyperglycemia may increase PGE_2 synthesis by β-cells, which would lead to impaired first-phase insulin response to glucose.

Recently, we observed that sodium salicylate does not restore first-phase insulin secretion in a type I diabetic patient early in the disease when circulating insulin levels could still be measured (Fig. 1). The patient was hyperglycemic but was not receiving exogenous insulin. He failed to respond to the same salicylate infusion rate that partially restored first-phase insulin secretion in type II diabetic patients matched for fasting glucose and insulin levels. This functional difference supports the notion that there is a profound pathophysiological difference in the nature of β-cell dysfunction in type I and type II diabetes, i.e., damage and eventual death in the former but a slower and potentially reversible process in the latter.

CONCLUSION

Defective recognition of glucose signals by the β-cell secretory apparatus—or glucose "non-sense"—in type II diabetic patients is highly specific, is at least partially reversible, and may represent homologous desensitization of the islet to glucose. An essential component of this secretory defect is secondary to hyperglycemia because it can be at least partially restored by normalization of glucose levels by exogenous insulin. This formulation neither requires nor precludes other primary β-cell abnormalities. Rather, I suggest that once hyperglycemia from whatever cause is manifest, glucose-induced glucose desensitization of the islet begins and exacerbates the first-phase secretory defect in glucose recognition. Desensitization to glucose is not likely to be a direct effect of glucose because restoration can be induced by several pharmacological maneuvers whose biochemical mechanisms are unrelated and because such restoration can take place in the presence of hyperglycemia. Elucidation of the biochemical mechanisms of islet desensitization to glucose will provide a deeper understanding of abnormal islet function and greatly needed insights into the pathogenesis and treatment of abnormal β-cell function in type II diabetes mellitus.

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