Phasic Insulin Release and Metabolic Regulation in Type 2 Diabetes

Stefano Del Prato,[1] Piero Marchetti,[1] and Riccardo C. Bonadonna[2]

Type 2 diabetes is a heterogeneous disorder due to prevalent insulin resistance associated with deficient insulin secretion or to a prevalent defect of insulin secretion associated with impaired insulin action. The definition is supported by the high frequency at which insulin resistance can be demonstrated in type 2 diabetic patients. Nonetheless, insulin resistance is not a sufficient mechanism to cause diabetes. Impaired β-cell function is a necessary defect in all conditions of impaired glucose regulation; however, it manifests itself in a different manner in fasting and glucose-stimulated conditions. In the fasting state, the basal insulin secretory rate increases as a function of the progressive decline in insulin action. As such, the fasting plasma insulin concentration is often taken as a marker for insulin sensitivity. After glucose challenge, a specific alteration of acute insulin release is an early and progressive defect. The latter might represent an intrinsic defect, but its continuous decline is affected by glucotoxicity and lipotoxicity. To understand the impact of β-cell dysfunction in type 2 diabetes on metabolic homeostasis, it is useful to consider the different phases of insulin secretion separately. Insulin secretion can be divided into basal (postabsorptive) and stimulated (postprandial) states. The former prevails during the interprandial phases and plays a major role during the overnight fast; the latter regulates glucose metabolism when carbohydrate is abundant and must be disposed of. Data in animals and humans support a crucial physiological role of first-phase insulin secretion in postprandial glucose homeostasis. This effect is primarily achieved in the liver, allowing prompt inhibition of endogenous glucose production and limiting the postprandial rise in plasma glucose level. In type 2 diabetes, loss of the early surge of insulin release is an early and quite common defect that may have a pathogenetic role in the development of postprandial hyperglycemia, possibly requiring specific therapeutic intervention. *Diabetes* 51 (Suppl. 1):S109–S116, 2002

From the [1]Department of Endocrinology and Metabolism, Section of Diabetes, University of Pisa, Pisa, Italy; and the [2]Section of Endocrinology and Metabolism, School of Medicine, University of Verona, Verona, Italy.

Address correspondence and reprint requests to sdelprato@immr.med.unipi.it.

Accepted for publication 31 May 2001.

S.D.P. has received honoraria for speaking engagements from Eli Lilly.

AIR, acute insulin response; EGP, endogenous glucose production; FFA, free fatty acid; HOMA, homeostatic model assessment; IFG, impaired fasting glucose; IGR, impaired glucose regulation; IGT, impaired glucose tolerance; IVGTT, intravenous glucose tolerance test; NFG, normal fasting glucose; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test.

The symposium and the publication of this article have been made possible by an unrestricted educational grant from Servier, Paris.

Type 2 diabetes is a heterogeneous disorder due, according to the American Diabetes Association Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (1), to prevalent insulin resistance associated with deficient insulin secretion or to a prevalent defect of insulin secretion associated with impaired insulin action. The definition is supported by the high frequency at which insulin resistance can be demonstrated in type 2 diabetic patients. In the setting of the Insulin Resistance and Atherosclerosis Study, Haffner et al. (2) reported that insulin resistance was present in over 85% of the diabetic individuals enrolled in the study, with no difference among non-Hispanic and African-American patients. Similarly, no regional influence was apparent, suggesting that insulin resistance occurs independently of environmental effects.

Plasma glucose level after an overnight fast is a function of endogenous glucose production (EGP), particularly the rate of gluconeogenesis (3). Accordingly, impaired insulin action at the liver causes fasting hyperglycemia. Insulin resistance in muscle tissues is primarily responsible for reduced glucose utilization despite physiological elevation of the plasma insulin concentration (3). The underlying mechanisms for impaired insulin action include cellular defects in postreceptor signaling, glucose transport, and/or regulatory enzymes of intracellular glucose metabolism (3,4).

Nonetheless, insulin resistance is not a sufficient mechanism to cause diabetes. Impaired insulin action can be demonstrated in obese subjects with normal glucose tolerance (NGT) (5) as well as in relatives of type 2 diabetic patients (6–8). We have recently analyzed the metabolic features of individuals with NGT (n = 126) as well as of three subgroups with impaired glucose regulation (IGR): *1*) individuals with impaired fasting glucose (IFG) but NGT (2-h post–oral glucose tolerance test [OGTT] ≤140 mg/dl; IFG/NGT; n = 8), *2*) individuals with impaired glucose tolerance (IGT) but normal fasting glucose (NFG) (NFG/IGT; n = 38), and *3*) individuals with both IFG and IGT (IFG/IGT; n = 15). A 75-g OGTT was performed in all subjects for determination of plasma glucose, insulin, and C-peptide concentration (9). The curves of plasma C-peptide concentration were then analyzed with a minimal model of glucose-induced C-peptide/insulin secretion for estimation of basal and post–oral glucose insulin secretion, and β-cell secretory capacity was expressed as the β-index (10). Insulin sensitivity (homeostatic model assessment [HOMA] insulin resistance index) was higher in IFG/NGT subjects (3.78 ± 0.78) and NFG/IGT subjects

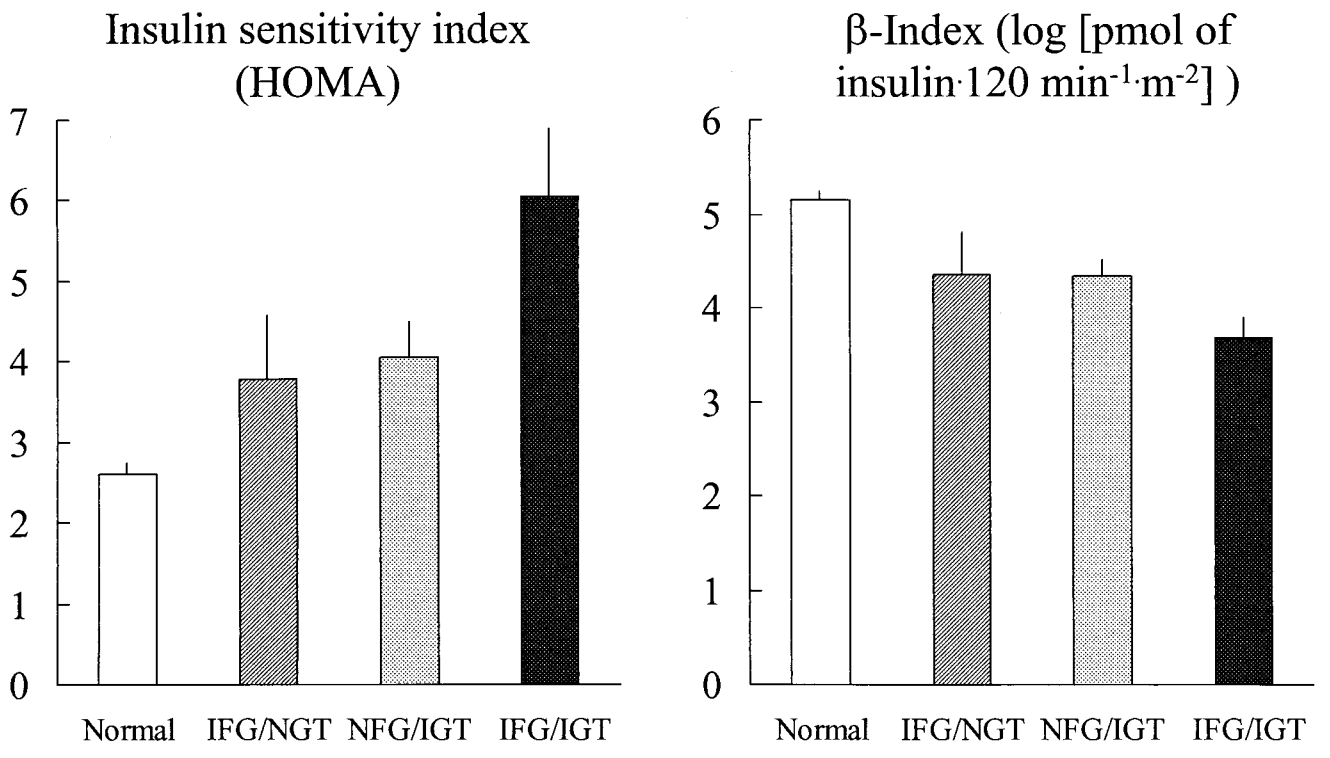

FIG. 1. Insulin resistance (HOMA) and insulin secretion (OGTT-derived β-index) in individuals with IFG but NGT (2-h post-OGTT ≤140 mg/dl; IFG/NGT; *n* = 8), individuals with IGT and NFG (NFG/IGT; *n* = 38), and individuals with both IFG and IGT (IFG/IGT; *n* = 15).

(4.05 ± 0.43; $P < 0.05$ vs. normal) compared with normal subjects (2.6 ± 0.1; $P < 0.01$ for both) (Fig. 1). A more severe impairment of insulin sensitivity was apparent in IFG/IGT subjects (6.04 ± 0.86; $P < 0.05$ vs. normal and NFG/IGT subjects). Basal insulin secretion increased as a function of the HOMA value across the different groups of glucose regulation (normal: 1.8 ± 0.1; IFG/NGT: 2.3 ± 0.3; NFG/IGT: 2.3 ± 0.2; and IFG/IGT: 2.7 ± 0.3 units · min^{-1} · m^{-2}; $P < 0.01$ vs. normal subjects). The β-index progressively decreased moving from normal subjects (5.15 ± 0.09 log [pmol insulin · 120 min^{-1} · m^{-2}]) to IFG/NGT subjects (4.35 ± 0.49) and NFG/IGT subjects (4.34 ± 0.18), to IFG/IGT subjects (3.68 ± 0.25; all $P < 0.05$ vs. normal subjects) (Fig. 1). None of these differences were influenced by age, sex, or BMI. Therefore, in Caucasians, IGR is associated with defects of both insulin secretion and insulin action with no apparent difference between isolated IFG and isolated IGT. The combination of basal and post-OGTT glucose impairment is associated with a further deterioration of both functions.

In our study, overall insulin secretion was assessed with no distinction between early- and second-phase insulin secretion. This may be of interest because a blunted early-phase insulin response to an intravenous glucose tolerance test (IVGTT) is common in all subjects with fasting plasma glucose ≥6.4 mmol/l (11). Impaired acute insulin secretion to glucose-dependent arginine stimulation (12) has been recently described in postmenopausal IGT women. More interestingly, longitudinal studies have indicated that early-phase insulin secretion is an independent predictor of the progression from NGT to IGT. In the San Antonio Heart Study (13), both a high fasting insulin concentration (a surrogate marker of insulin resistance) and a low incremental 30-min insulin concentration (an indicator of early-phase insulin response) were independent predictors of the progression of NGT to IGT in the Mexican-American population. Among a cohort of 348 women aged 50 years on entering a 12-year prospective study, the incidence of diabetes was higher in those who initially had higher fasting plasma glucose and insulin concentrations and lower early insulin release in response to IVGTT (14). In particular, 17.1% of the women who had early insulin response within the lowest quintile developed diabetes. The insulinogenic index is calculated as the ratio of the increment of plasma insulin to glucose concentration 30 min after an OGTT, and it provides a parameter of early insulin response (15). Development of diabetes occurs more frequently in individuals with low values of the insulinogenic index than in normal insulin responders. The prevalence of low insulin responders (i.e., low insulinogenic index) is higher in subjects with a family history of diabetes. Finally, low insulin response is more frequent in subjects who have a strong genetic background for diabetes, such as cotwins of monozygotic diabetic twins and offspring of conjugal diabetic patients (15). Although the 30-min plasma insulin increment and the insulinogenic index obtained with an OGTT are correlated with the acute insulin response (AIR) obtained with an IVGTT (15,16), this correlation is not very strong (17).

More recently, longitudinal data have been reported from 17 Pima Indians in whom glucose tolerance deteriorated from normal (NGT) to impaired (IGT) to diabetes over a 5-year follow-up (18). Transition from NGT to IGT was associated with an increase in body weight, a decline in insulin-stimulated glucose disposal, and a reduction in AIR to intravenous glucose. Progression from IGT to

diabetes was associated with a modest worsening in insulin sensitivity but a much greater decline in AIR. Thirty-one subjects who retained NGT over a similar period also gained weight and had further deterioration of their insulin sensitivity, but their AIR increased. A further analysis of data has indicated that, in Pima Indians, a low insulin sensitivity and a low AIR (i.e., an early-phase insulin response to glucose) are independent and additive predictors of the progression from NGT to IGT and from IGT to overt diabetes, suggesting that the two defects play a pathogenic role at each stage of IGR (19).

The nature of the very specific defect of AIR is not understood. In particular, it is not clear if this represents a primary or acquired alteration of β-cell function. Glucose toxicity can hamper AIR, as elegantly shown several years ago by Weir's group (20). In humans, a 72-h glucose infusion that induced moderate hyperglycemia (~110 mg/dl) did not affect insulin secretion measured during a hyperglycemic clamp (21). After a 72-h glucose infusion, the early (282 ± 48 vs. 168 ± 60 pmol/l), late (612 ± 102 vs. 276 ± 48 pmol/l), and total (582 ± 102 vs. 264 ± 48 pmol/l) plasma insulin responses were significantly greater. Thus, in healthy young subjects with no family history of diabetes and, presumably, no genetic β-cell abnormality, chronic (72-h) physiological hyperglycemia causes a marked potentiation of both early and late plasma insulin responses to the acute increase in plasma glucose concentration. These results may appear to be in contrast to animal studies where a similar duration (72 h) of hyperglycemia was shown to impair insulin secretion (22,23). However, in those studies, glucose was infused chronically in rats that had undergone a partial pancreatectomy or had received low-dose streptozotocin to reduce β-cell mass. These results indicate that either a greater degree or a longer duration of hyperglycemia is needed to affect β-cell function of normal individuals. Alternatively, a predisposing background should be hypothesized to account for the negative effects of even a moderate increase in plasma glucose concentration on insulin secretion. From this point of view, it is of interest that alteration of the insulin-signaling pathway at the level of the β-cell is associated with impaired β-cell function (24). Pancreatic β-cell insulin receptor knockout has been achieved in mice using the Cre-loxP–mediated strategy (25). These animals developed a selective loss of acute insulin release in response to glucose, resulting in a progressive impairment of glucose tolerance (25). Impairment of insulin action at the level of peripheral tissues may also exert an indirect detrimental effect on β-cell function. In this regard, accelerated lipolysis resulting in elevated plasma free fatty acid (FFA) levels, a common feature in insulin-resistant states, may be important. In our laboratory, we analyzed the effect of elevated FFA concentrations on insulin secretion from human islets by perifusion (26). Basal insulin release was 43.8 ± 6.4 and 34.8 ± 5.9 pmol/min in control and FFA-exposed islets, respectively. Preculture with high concentrations of FFAs caused a marked decrease of insulin secretion, which was mainly accounted for by a reduction in early-phase insulin release. The amount of insulin released during the first 10 min of perifusion with 16.7 mmol/l glucose was 66.6 ± 39.6 and 19.7 ± 7.2 pmol/min from control and FFA-exposed islets, respectively ($P < 0.05$). Impaired insulin secretion was associated with an FFA-induced reduction in glucose utilization and oxidation, suggesting that lipotoxicity may act, at least in part, through activation of the classic Randle cycle. This interpretation is supported by the finding that insulin response to secretagogues other than glucose, such as arginine and glibenclamide, was not affected by incubation in the presence of high concentrations of FFA. Interestingly, insulin secretion from human islets from a type 2 diabetic patient that were incubated at a low glucose concentration presented the same loss of early-phase insulin secretion (Fig. 2).

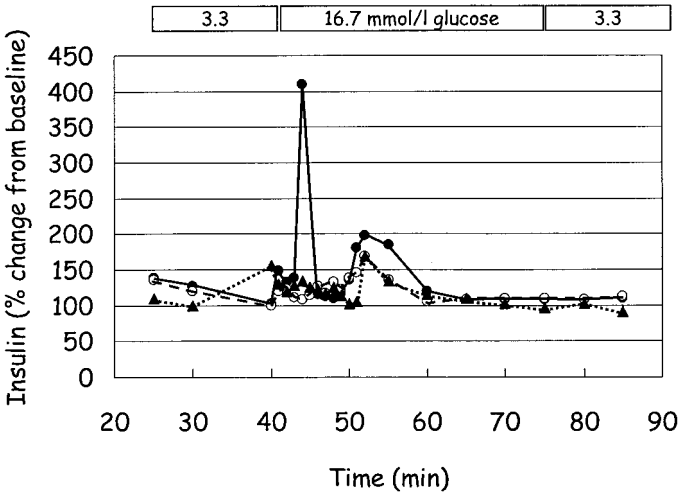

FIG. 2. Percentage increase of insulin secretion from human pancreatic islets incubated in the absence (●, control study) or presence of 2.0 mmol/l FFA (○) (oleate/palmitate 2:1) and human islets from the pancreas of a patient with type 2 diabetes (▲).

In summary, impaired β-cell function is a necessary defect in all conditions of IGR; however, it manifests itself in a different manner in fasting and glucose-stimulated conditions. In the fasting state, the basal insulin secretory rate increases as a function of the progressive decline in insulin action. As such, fasting plasma insulin concentration is often taken as a marker for insulin sensitivity. After a glucose challenge, a specific alteration of acute insulin release is an early and progressive defect. The latter might represent an intrinsic defect, but its continuous decline is affected by glucotoxicity and lipotoxicity.

To understand the impact of β-cell dysfunction in type 2 diabetes on metabolic homeostasis, it may be useful to consider the different phases of insulin secretion separately. For the sake of clarity, insulin secretion can be divided into basal (postabsorptive) and stimulated (postprandial) states. The former prevails during the interprandial phases and plays a major role during the overnight fast; the latter regulates glucose metabolism when carbohydrate is abundant and must be disposed of.

BASAL INSULIN SECRETION

Adequate basal insulin secretion is important in glucose regulation both in the liver and in the peripheral tissues (muscle and adipose tissue). A major effect is EGP modulation, which is exquisitely sensitive to small changes in portal insulin concentration. In a dose-response study in healthy subjects, an increase in portal insulin concentration of 5 μU/ml above baseline resulted in up to 50%

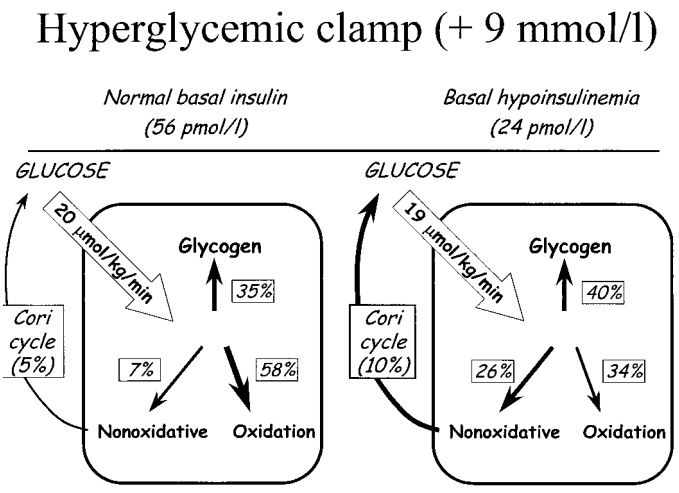

FIG. 3. Effect of basal insulinization on intracellular glucose metabolism and activity of Cori cycle during a hyperglycemic clamp (160 mg/dl above baseline) performed during somatostatin infusion with or without basal plasma insulin replacement.

suppression of hepatic glucose production (27). In contrast, a similar inhibition of hepatic glucose production in type 2 diabetic patients was reached only with a much greater increment in the portal levels of insulin (27). In view of the well-known direct relationship between basal hepatic glucose production and fasting plasma glucose concentration, adequate overnight insulin secretion is needed to ensure euglycemia in the postabsorptive state. A recent matter of discussion has been whether EGP modulation by insulin is a direct effect (i.e., regulation of enzyme activity) or indirect via inhibition of lipolysis and FFA supply to the liver (28). Although the issue is not completely solved, it is important to recall the potent effect of a modest increase in fasting plasma insulin concentration in suppressing FFA release (27). In type 2 diabetic patients, the combination of insulin resistance and inadequate basal insulin secretion to compensate for the defect in insulin action may well account for excessive EGP.

The key role of basal insulin secretion on an integrated regulation of glucose homeostasis can be fully appreciated in normal subjects rendered hyperglycemic by means of a hyperglycemic clamp (180 mg/dl above baseline) carried out in combination with a somatostatin infusion (29). The study was repeated twice: in the first case, relative hypoinsulinemia was induced, while in the second, basal insulin concentrations were restored by appropriate exogenous insulin infusion. Under this condition, glucose utilization proceeds mainly by mass effect of glucose concentration (glucose mass effect), and it is not different in both conditions (Fig. 3). However, when intracellular glucose disposition is monitored by a dual isotope technique (30), a major regulatory role of basal insulin becomes apparent. As summarized in Fig. 3, basal hypoinsulinemia was associated with a reduction in glucose oxidation, a concomitant increase of anaerobic glycolysis, activation of the Cori cycle, and less effective suppression of EGP (28). The latter was directly correlated with the Cori cycle activity ($r = 0.61$; $P < 0.05$). Moreover, plasma FFA concentrations were higher, and lipid oxidation was increased. In this case too, plasma FFA concentrations and EGP were directly related ($r = 0.59$; $P < 0.05$).

These observations suggest that the basal level of insulinemia is important in modulating the intracellular fate of the glucose taken up by peripheral tissues and that a dysfunction in basal insulin secretion may contribute to the accelerated release of FFAs and lactate (31). The latter is a preferential gluconeogenic substrate, and the former provides the energy required for driving gluconeogenesis; the final result is enhanced EGP and fasting hyperglycemia.

Correction of absolute or relative hypoinsulinemia in type 2 diabetes is thus a rational therapeutic approach, and it has been tested experimentally. Type 2 diabetic patients with secondary failure to oral antidiabetic agents were studied before and after adding a preprandial subcutaneous injection of long-acting insulin while maintaining preprandial administration of a sulfonylurea. In agreement with the hypothesis on the regulatory role of basal insulinemia, improvement in the postabsorptive concentration of plasma insulin was associated with a reduction in basal hepatic glucose production, fasting plasma glucose, and FFA levels (32). Moreover, the improvement of basal glucose levels was associated with a positive influence on the daily plasma glucose profile, as indicated by a positive correlation between the decrease in fasting plasma glucose and the reduction in 24-h glucose levels ($r = 0.90$; $P < 0.01$). This finding was confirmed in type 1 diabetic patients, in whom appropriate restoration of basal insulin levels improves fasting plasma glucose levels and the daily plasma glucose profile (33).

POSTPRANDIAL INSULIN SECRETION

The rise in plasma insulin level that follows the ingestion of food (carbohydrate in particular) stimulates glucose uptake in peripheral tissues (mainly muscle) and suppresses EGP. The normal biological action of insulin on these tissues limits the fluctuation of plasma glucose level within a fairly narrow range. Most current knowledge of the physiological actions of insulin was derived from glucose clamp studies, in which euglycemia is maintained while the plasma insulin concentration is increased to a predetermined value. Despite the usefulness of this technique, it must be recognized that the square-wave increase of plasma insulin concentration created by exogenous infusion is different from the physiological response of the β-cell to an increase in plasma glucose concentration. This physiological response is biphasic in nature. On stimulation, the β-cell responds with a prompt but short-lived (0–10 min) release of insulin (first phase) followed by a steady and longer-lasting increase in plasma insulin concentration (second phase).

In the early stages of type 2 diabetes or in patients with IGT, first-phase insulin release is almost invariably lost, despite the common enhancement of second-phase insulin secretion as previously discussed. Although the physiological and metabolic implications of the biphasic β-cell response are not yet fully understood, available evidence suggests a physiological role for the dynamics of insulin secretion and the acute surge of insulin release into the portal circulation in regulating glucose homeostasis.

A strong negative relationship has been demonstrated between the first-phase insulin release and the initial glucose increment after starting a glucose infusion (34). This finding suggested that an early surge of insulin

secretion could limit the rise in blood glucose concentration. Furthermore, the larger the insulin surge, the longer the effect on glucose homeostasis. In patients with IGT, there is an inverse correlation between plasma insulin levels 30 min after an oral glucose load and the plasma glucose concentration at 2 h (35), suggesting that the persistence of early insulin response has implications for glucose tolerance by ensuring more physiological plasma glucose levels.

The amount, time course, and anatomical site (i.e., portal vein) of insulin release during first-phase secretion suggest a likely effect on the liver rather than on peripheral tissues. This view is supported by the finding in dogs that both first- and second-phase insulin secretion are crucial in counterbalancing the hyperglycemic effect of a glucagon infusion (36,37). In particular, restoration of the early increase in plasma insulin level, even in the absence of the second phase, reduced the glucagon-mediated rise in plasma glucose concentration (36) by a reduction in gluconeogenesis (37).

Human data are also available to support a crucial role for first-phase insulin secretion in the modulation of hepatic glucose production. Hepatic glucose output and tissue glucose uptake have been measured in normal subjects in hyperglycemic clamp studies (38). The acute elevation of plasma glucose concentration and the subsequent biphasic insulin release were associated with progressive suppression of hepatic glucose production and an increase in glucose disposal by the body tissues. Abolition of first-phase insulin secretion by somatostatin and appropriate insulin replacement was not associated with changes in glucose utilization. In contrast, the impact on suppression of hepatic glucose production was dramatic, with the liver releasing glucose at a higher rate despite the presence of hyperglycemia and hyperinsulinemia. The alteration was a direct consequence of the specific defect because restoration of first-phase insulin secretion was followed by complete normalization of hepatic glucose production.

These results are in agreement with the correlation between the plasma insulin concentration 30 min after an oral glucose load and the rate of glucose appearance (including hepatic glucose production) reported in patients with IGT (35). Furthermore, an inverse correlation between the rate of appearance of glucose and the insulin/glucagon ratio was found in the same subjects. This has particular relevance to the degree of hyperglycemia in type 2 diabetic patients after the ingestion of a mixed meal. In the postprandial phase, plasma glucagon concentration remains higher than in normal individuals despite a normal or increased plasma insulin concentration, and an inability to suppress EGP rather than impaired glucose disposal seems to account for hyperglycemia (39). Not only are plasma glucagon concentrations higher in type 2 diabetic patients, but preliminary reports indicate that the response of hepatic glucose production to increasing rates of glucagon infusion is consistently higher in these individuals than in matched normal individuals (40), suggesting an increased sensitivity to the biological action of the hormone.

Although the biphasic response is fully appreciated with an intravenous glucose challenge, a rapid increase in plasma insulin levels after ingestion of an oral glucose load seems to be essential for NGT. Calles-Escandon and Robbins (41) used somatostatin infusion to inhibit the early insulin response to an OGTT in normal individuals. The loss of the early phase of insulin secretion was associated with a deterioration of glucose tolerance, as indicated by a lower K value (1.9 ± 0.4 vs. 1.1 ± 0.3, $P < 0.001$) and much larger glycemic excursion. Surprisingly, glucose-induced thermogenesis was reduced in association with the loss of the early phase of insulin release. Using a more sophisticated technique, Basu et al. (42) studied nondiabetic individuals during somatostatin inhibition of endogenous insulin secretion, where exogenous insulin was infused so as to mimic postprandial insulin profiles of a typical normal or diabetic individual. Simultaneously, glucose was infused in a pattern and amount that mimicked the systemic delivery rate normally observed after the ingestion of 50 g glucose. The delayed pattern of insulin delivery (i.e., loss of early-phase insulin secretion) was associated with a higher ($P < 0.05$) glucose concentration and a prolonged duration of hyperglycemia. This alteration was mainly due to altered suppression of EGP.

Furthermore, after the ingestion of a mixed meal, plasma insulin concentration increased rapidly with a 30-min peak (43). The quick rise in plasma insulin concentration was associated with a marked decrease in the glucagon/insulin ratio, glycogen accretion in the liver, and concomitant suppression of EGP.

If the loss of early insulin release plays a major role in the pathogenesis of postprandial hyperglycemia, therapeutic intervention capable of restoring it should be able to improve glucose tolerance in type 2 diabetic patients. The study by Bruce et al. (44) was designed to test whether correcting the deficiency in early prandial insulin secretion with a physiological dose of exogenous insulin would have a beneficial effect on postprandial glucose excursions of type 2 diabetic patients. For this purpose, the same amount of insulin was given intravenously at mealtime to diabetic patients *1*) over 30 min at the beginning of a meal (i.e., restoration of early insulin increase), *2*) as the same insulin profile but delayed by 30 min, and *3*) as a constant infusion over the entire duration of the study. A significant improvement in postprandial glucose tolerance was apparent only with early administration of insulin. Early insulin augmentation resulted in elevated plasma insulin levels initially, but subsequent insulin and C-peptide levels were lower than those in the control studies.

These results have been replicated in our laboratory comparing the effect of similar doses (0.075 units/kg lean body mass) of regular insulin and the insulin analog lispro given subcutaneously to type 2 diabetic patients before a 50-g OGTT (45). The fast-acting insulin analog lispro provides a therapeutic tool for assessing the metabolic outcome of restoration of an early rise in plasma insulin levels after the ingestion of the oral glucose load. In spite of comparable incremental areas under the curve, the time course of plasma insulin concentration was very different. After injection of regular insulin, plasma insulin peaked at 120 min, whereas with lispro, the peak occurred at 60 min. Plasma insulin concentration during the last 3 h of the study, however, was lower with lispro compared with

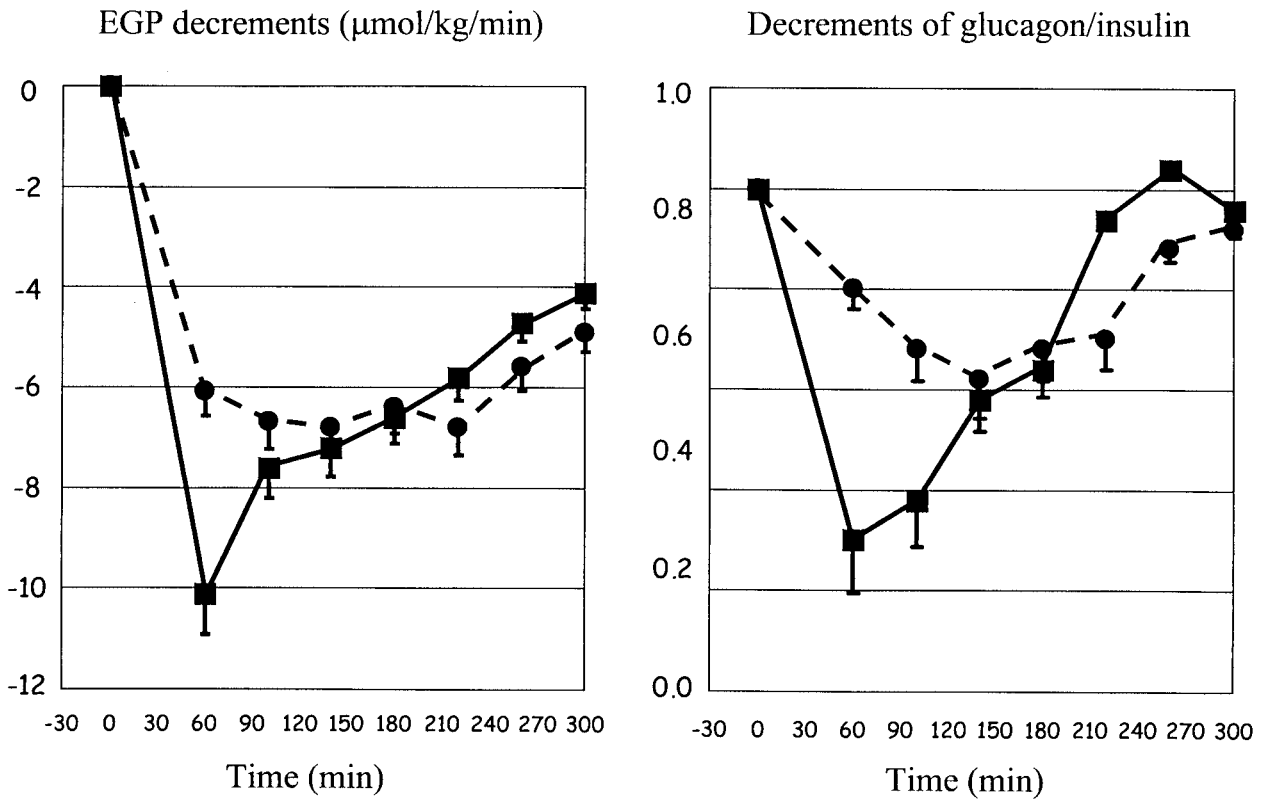

FIG. 4. Decrements of endogenous glucose production and glucagon/insulin ratio after a 50-g OGTT preceded by regular (●) and human insulin analog lispro (■) (both 0.075 units/kg of fat-free mass).

regular insulin. The plasma glucose incremental area under the curve was 46% lower with lispro (715 ± 109 vs. 389 ± 109 mmol/300 min; $P < 0.01$). The incremental area under the curve of plasma C-peptide also was lower with lispro ($P < 0.01$). This finding may be interpreted as a sparing effect on β-cell function due to prevention of excessive glucose rise. The lower plasma C-peptide levels in the late phase of the study were associated with lower glucose and insulin concentrations. This finding is in keeping with the direct correlation between the 120-min post-OGTT plasma glucose and insulin levels and suggests that any pharmacological intervention that restores early-phase insulin response represents a potential way of avoiding chronic hyperglycemia/hyperinsulinemia.

The study was carried out in combination with a double-tracer technique (3-[^{3}H]glucose continuous infusion plus U-[^{13}C]glucose spiking of an oral glucose load) for calculation of the rates of glucose utilization and production. There was no difference between the two studies in the rate of appearance of the ingested glucose nor in overall rate of glucose disposal. During the initial 90 min, however, EGP was suppressed in a prompter and more profound manner when lispro was administered ($P < 0.05$), whereas there was no difference in the late prandial phase. The more rapid increase in plasma insulin concentration was not associated with a greater suppression of plasma glucagon concentration. Nonetheless, if the glucagon/insulin ratio is calculated, a parallel time course was apparent with EGP suppression (Fig. 4). Finally, the study was carried out with intermittent measurement of respiratory gas exchange, allowing calculation of substrate oxidation. In spite of there being no difference in the rate of glucose utilization, the early rise in plasma insulin concentration was associated with a significant effect on energy metabolism. Lispro administration was indeed associated with a greater stimulation of carbohydrate oxidation and reciprocal larger inhibition of lipid oxidation. Because there was no significant difference in plasma FFA concentration between the two studies, it is unreasonable to suggest that less provision of FFA to metabolically active tissues accounts for the greater carbohydrate oxidation. Rather, the reduction in lipid oxidation could be interpreted as a backward activation of the Randle cycle. The difference between glucose utilization and glucose oxidation provides a measure of nonoxidative glucose metabolism, which was lower with restoration of an early rise in plasma insulin concentrations. Although glycogen synthesis accounts for much of the nonoxidative glucose metabolism, nonoxidative glycolysis is exceedingly high in type 2 diabetic patients (4), suggesting that appropriate insulinization may funnel more glucose into the Krebs cycle, reduce the activity of nonoxidative glycolysis, and, by competition, reduce lipid oxidation.

TABLE 1
Metabolic implications of loss of early-phase insulin response to nutrients

Early feature in the history of impaired glucose regulation
Associated with enhanced hyperglycemic effect of glucagons
Associated with enhanced glucagon-stimulated gluconeogenesis
Impaired suppression of endogenous glucose production after nutrient ingestion
Inversely correlated with late postprandial hyperglycemia
Directly correlated with late postprandial hyperinsulinemia

In summary, data for animals and humans support a crucial physiological role of first-phase insulin secretion in postprandial glucose homeostasis (Table 1). This effect is primarily achieved in the liver, allowing prompt inhibition of endogenous glucose production and limiting the postprandial rise in plasma glucose level. In type 2 diabetes, loss of the early surge of insulin release is an early and quite common defect that may have a pathogenetic role in the development of postprandial hyperglycemia and may require specific therapeutic intervention.

REFERENCES

1. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 23 (Suppl. 1):S4–S19, 2000
2. Haffner S, Howard G, Mayer E, Bergman RN, Rewers M, Mykkanen L, Karter AJ, Hamman R, Saad MF: Insulin sensitivity and acute insulin response in African-Americans, non-Hispanic whites, and Hispanics with NIDDM: the Insulin Resistance Atherosclerosis Study. *Diabetes* 47:63–69, 1997
3. DeFronzo RA, Bonadonna RC, Ferrannini E: Pathogenesis of NIDDM: a balanced overview. *Diabetes Care* 15:318–368, 1992
4. Del Prato S, Bonadonna RC, Bonora E, Gulli G, Solini A, Shank M, DeFronzo RA: Characterization of cellular defect of insulin action in type II (non-insulin-dependent) diabetes mellitus. *J Clin Invest* 91:484–494, 1993
5. Del Prato S, Enzi G, Vigili de Kreutzenberg S, Lisato G, Riccio A, Maifreni L, Iori E, Zurlo F, Sergi G, Tiengo A: Insulin regulation of glucose and lipid metabolism in massive obesity. *Diabetologia* 33:228–236, 1990
6. Lillioja S, Mott DM, Howard BV, Bennett PH, Yki-Jarvinen H, Freymond D, Nyomba BL, Zurlo F, Swinburn B, Bogardus C: Impaired glucose tolerance as a disorder of insulin action: longitudinal and cross-sectional studies in Pima Indians. *N Engl J Med* 318:1217–1225, 1988
7. Eriksson J, Franssila-Kallunki A, Ekstrand A, Saloranta C, Widen E, Schalin C, Groop L: Early metabolic defects in persons at increased risk of type 2 diabetes. *N Engl J Med* 321:337–343, 1989
8. Gulli G, Ferrannini E, Stern M, Haffner S, DeFronzo RA: The metabolic profile of NIDDM is fully established in glucose-tolerant offspring of two Mexican-American NIDDM parents. *Diabetes* 41:1575–1586, 1992
9. Bonadonna RC, Cretti A, Brunato B, Cirillo R, Del Prato S: Metabolic features of impaired glucose regulation in Caucasians. *Diabetologia* 43 (Suppl. 1):A16, 2000
10. Cretti A, Lehtovirta M, Bonora E, Brunato B, Zenti MG, Tosi F, Caputo M, Caruso B, Groop LC, Muggeo M, Bonadonna RC: Assessment of beta-cell function during the oral glucose tolerance test by a minimal model of insulin secretion. *Eur J Clin Invest* 31:405–416, 2001
11. Brunzell JD, Robertson RP, Lerner RL, Hazzard WR, Ensinck JW, Bierman EL, Porte D Jr: Relationship between fasting plasma glucose levels and insulin secretion during intravenous glucose tolerance. *J Clin Endocrinol Metab* 42:222–229, 1976
12. Larsson H, Ahren B: Islet dysfunction in insulin resistance involves impaired insulin secretion and increased glucagon secretion in postmenopausal women with impaired glucose tolerance. *Diabetes Care* 23:650–657, 2000
13. Haffner SM, Miettinen H, Gaskill SP, Stern M: Decreased insulin action and insulin secretion predict the development of impaired glucose tolerance. *Diabetologia* 39:1201–1207, 1996
14. Lundgren H, Bengtsson C, Blohmè G, Lapidus L, Waldeström J: Fasting serum insulin concentration and early insulin response as risk determinants for developing diabetes. *Diabet Med* 7:407–413, 1990
15. Kosaka K, Kuzuya T, Hagura R, Yoshinaga H: Insulin response to oral glucose load is consistently decreased in established non-insulin-dependent diabetes mellitus: the usefulness of decreased early insulin response as a predictor of non-insulin-dependent diabetes mellitus. *Diabet Med* 13:S109–S119, 1996
16. Davies MJ, Rayman G, Grenfell A, Gray IP, Day JL, Hales CN: Loss of the first-phase insulin response to intravenous glucose in subjects with persistent impaired glucose tolerance. *Diabet Med* 11:432–436, 1994
17. Hanson RL, Pratley RE, Bogardus C, Venkat Narayan KM, Roumain JM, Imperatore G, Fagot-Campagna A, Pettitt DJ, Bennett PH, Knowler WC: Evaluation of simple indices of insulin sensitivity and insulin secretion for use in epidemiologic studies. *Am J Epidemiol* 151:190–198, 2000
18. Weyer C, Bogardus C, Mott DM, Pratley RE: The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. *J Clin Invest* 104:787–794, 1999
19. Weyer C, Tataranni PA, Bogardus C, Pratley RE: Insulin resistance and insulin secretory dysfunction are independent predictors of worsening of glucose tolerance during each stage of type 2 diabetes development. *Diabetes Care* 24:89–94, 2001
20. Leahy JL, Bonner-Weir S, Weir GC: Beta-cell dysfunction induced by chronic hyperglycemia: current ideas on mechanism of impaired glucose-induced insulin secretion. *Diabetes Care* 15:442–455, 1992
21. Del Prato S, Leoanetti F, Simonson DC, Sheean P, Matsuda M, DeFronzo RA: Effect of sustained physiologic hyperinsulinaemia and hyperglycaemia on insulin secretion and insulin sensitivity in man. *Diabetologia* 37:1025–1035, 1994
22. Rossetti L, Shulman GI, Zawalich W, DeFronzo RA: Effect of chronic hyperglycemia on in vivo insulin secretion in partially pancreatectomized rats. *J Clin Invest* 80:1037–1044, 1987
23. Leahy JL: Natural history of beta cell dysfunction in NIDDM. *Diabetes Care* 13:992–1010, 1990
24. Porzio O, Federici M, Hribal ML, Lauro D, Accili D, Lauro R, Borboni P, Sesti G: The Gly972→Arg amino acid polymorphism in IRS-1 impairs insulin secretion in pancreatic beta cells. *J Clin Invest* 104:357–364, 1999
25. Kulkarni RN, Bruning JC, Winnay JN, Postic C, Magnuson MA, Kahn CR: Tissue-specific knockout of the insulin receptor in pancreatic beta cells creates an insulin secretory defect similar to that in type 2 diabetes. *Cell* 96:329–339, 1999
26. Lupi R, Del Guerra S, Fierabracci V, Marselli L, Masiello P, Patanè G, Boggi U, Mosca F, Purrello F, Del Prato S, Marchetti P: Lipotoxicity in human pancreatic islets and the effects of metformin. *Diabetes* 51 (Suppl. 1):S134–S137, 2002
27. Groop LC, Bonadonna RC, Del Prato S, Ratheiser K, Zyck K, Ferrannini E, DeFronzo RA: Glucose and free-fatty acid metabolism in non-insulin-dependent diabetes: evidence for multiple insulin resistance. *J Clin Invest* 84:205–213, 1989
28. Bergman RN: Non-esterified fatty acids and the liver: why is insulin secreted into the portal vein? *Diabetologia* 43:946–952, 2000
29. Del Prato S, Gulli G, Bonadonna RC: Effect of hyperglycemia on glucose metabolism: regulatory role of basal plasma insulin levels (Abstract). *Diabetes* 41 (Suppl. 1):188A, 1992
30. Bonadonna RC, Del Prato S, Bonora E, Gulli G, Solini A, DeFronzo RA: Effects of physiological hyperinsulinemia on the intracellular metabolic partition of plasma glucose. *Am J Physiol* 265:E943–E953, 1993
31. Avogaro A, Toffolo G, Miola M, Valerio A, Tiengo A, Cobelli C, Del Prato S: Intracellular lactate- and pyruvate-interconversion rates are increased in muscle tissue of non-insulin-dependent diabetic individuals. *J Clin Invest* 98:108–115, 1996
32. Del Prato S, Vigili de Kreutzenberg S, Riccio A, Maifreni L, Duner E, Lisato G, Iavicoli M: Partial recovery of insulin secretion and action after combined insulin-sulfonylurea treatment in type 2 (non-insulin-dependent) diabetic patients with secondary failure to oral agents. *Diabetologia* 33:688–695, 1990
33. Riccio A, Avogaro A, Valerio A, Zappella A, Tiengo A, Del Prato S: Improvement of basal hepatic glucose production and fasting hyperglycemia of type 1 diabetic patients treated with human recombinant ultralente insulin. *Diabetes Care* 17:535–540, 1994
34. Bruce DG, Storlien LH, Furler SM, Chisholm DJ: Cephalic phase metabolic responses in normal weight adults. *Metabolism* 36:721–725, 1987
35. Mitrakou A, Kelley D, Mokan M, Veneman T, Pangburn T, Reilly J, Gerich J: Role of reduced suppression of glucose production and diminished early insulin release in impaired glucose tolerance. *N Engl J Med* 326:22–29, 1992
36. Steiner KE, Mouton SM, Bowels CR, Williams PE, Cherrington AD: The relative importance of first- and second-phase insulin secretion in countering the action of glucagon on glucose turnover in the conscious dog. *Diabetes* 31:964–972, 1982
37. Steiner KE, Mouton SM, Williams PE, Lacy WW, Cherrington AD: Relative importance of first- and second-phase insulin secretion in glucose homeostasis in conscious dog. II. Effects on gluconeogenesis. *Diabetes* 35:776–784, 1986
38. Luzi L, DeFronzo RA: Effects of loss of first-phase insulin secretion on hepatic glucose production and tissue glucose disposal in humans. *Am J Physiol* 257:E241–E246, 1989
39. Shank M, Solini A, Barzilai N: Peripheral and hepatic glucose metabolism following mixed meal ingestion in NIDDM (Abstract). *Diabetes* 39 (Suppl. 1):118A, 1990
40. Matsuda M, Consoli A, Bressler P, DeFronzo RA, Del Prato S: Sustained response of hepatic glucose production (HGP) to glucagon in type 2 diabetic subjects (Abstract). *Diabetologia* 35 (Suppl. 1):A37, 1992

41. Calles-Escandon J, Robbins DC: Loss of early phase of insulin release in humans impairs glucose tolerance and blunts thermic effect of glucose. *Diabetes* 36:1167–1172, 1987
42. Basu A, Alzaid A, Dinneen S, Caumo A, Cobelli C, Rizza RA: Effects of a change in the pattern of insulin delivery on carbohydrate tolerance in diabetic and nondiabetic humans in the presence of differing degrees of insulin resistance. *J Clin Invest* 97:2351–2361, 1996
43. Taylor R, Magnusson I, Rothman DL, Cline GW, Caumo A, Cobelli C, Shulman GI: Direct assessment of liver glycogen storage by ^{13}C nuclear magnetic resonance spectroscopy and regulation of glucose homeostasis after a mixed meal in normal subjects. *J Clin Invest* 97:126–132, 1996
44. Bruce DG, Chisholm DJ, Storlien LH, Kraegen EW: Physiological importance of deficiency in early prandial insulin secretion in non–insulin-dependent diabetes. *Diabetes* 37:736–744, 1988
45. Bruttomesso D, Pianta A, Mari A, Valerio A, Marescotti MC, Avogaro A, Tiengo A, Del Prato S: Restoration of early rise in plasma insulin levels improves the glucose tolerance of type 2 diabetic patients. *Diabetes* 48:99–105, 1999