Is Reduced First-Phase Insulin Release the Earliest Detectable Abnormality in Individuals Destined to Develop Type 2 Diabetes?

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Insulin is released from the pancreas in a biphasic manner in response to a square-wave increase in arterial glucose concentration. The first phase consists of a brief spike lasting ~10 min followed by the second phase, which reaches a plateau at 2–3 h. It is widely thought that diminution of first-phase insulin release is the earliest detectable defect of β-cell function in individuals destined to develop type 2 diabetes and that this defect largely represents β-cell exhaustion after years of compensation for antecedent insulin resistance. In this article, the origins of these concepts are reviewed and recent evidence is presented suggesting that reductions in both phases of insulin release are equally early, that they precede insulin resistance other than that simply due to obesity, and that they therefore may represent the primary genetic risk factor predisposing individuals to type 2 diabetes. *Diabetes* 51 (Suppl. 1): S117–S121, 2002

The kinetics of insulin release and its implications for normal physiology and the pathogenesis of type 2 diabetes were the main themes of this symposium. It has been known for nearly 40 years that insulin secretion is biphasic (1) (i.e., in response to a square-wave hyperglycemic stimulus to either the in vitro perfused rat pancreas or the in vivo human pancreas) and that insulin concentrations in perfusate and plasma increase rapidly to a peak at 2–4 min, decrease to a nadir at 10–15 min, and then gradually increase progressively to a pseudo-steady state at 2–3 h. The initial spike response is generally referred to as first-phase insulin release, and the subsequent increase in insulin secretion is considered to represent the second-phase insulin release.

The earliest detectable defect in β-cell function is commonly thought to be a reduction in first-phase insulin release (2). This concept arose largely based on cross-sectional studies of individuals with various degrees of glucose tolerance that examined only first-phase insulin responses after intravenous injection of insulin. These studies found that first-phase insulin was reduced in individuals with plasma glucose in upper ranges of normal and was essentially absent in people with fasting hyperglycemia (3,4). The concept received further support from studies of people with impaired glucose tolerance (IGT), a precursor of type 2 diabetes, showing that these individuals generally had reduced plasma insulin levels at 30 min after glucose ingestion and "normal or increased" plasma insulin levels at 120 min (5). The assumption has been generally made that the 30-min response reflected first-phase insulin release, whereas the 120-min response reflected second-phase insulin release. Because insulin released early after glucose ingestion has been shown to be a key determinant of subsequent plasma glucose responses (6,7), it became widely accepted that reduced first-phase insulin release is responsible for the development of IGT.

It should be noted, however, that the so-called "normal or increased" 120-min plasma insulin levels may not have been appropriate for the prevailing glycemic stimulus (8). Thus, if these late insulin responses reflect second-phase insulin release, this phase of insulin secretion may also have been reduced.

A related issue for individuals interested in the pathogenesis of type 2 diabetes is the debate as to whether insulin resistance or impaired β-cell function is the primary defect. By primary defect, the underlying genetic defect is meant. It seems pretty well established that type 2 diabetes is a polygenic disorder in which both hereditary and environmental or acquired factors are involved (9), and both of these factors can affect β-cell function and insulin sensitivity (10,11). From the elegant studies of Bergman et al. (12) and Kahn et al. (13), we know that the normal islet adjusts its function to compensate for insulin resistance, and, thus, in interpreting the appropriateness of insulin secretion, we must take into consideration not only the stimulus (i.e., plasma glucose level), but also the prevailing insulin sensitivity. For example, during a hyperglycemic clamp experiment in which plasma glucose was increased to comparable levels in a lean and an obese individual, plasma insulin responses in the lean individual compared with those of the obese individual would be inappropriate and signify impaired β-cell function.

Unfortunately, in the past, these variables were generally not taken into consideration and because of this, the concept that insulin resistance precedes β-cell failure in the progression to type 2 diabetes became widely believed (14) and consequently so did the concept that insulin resistance was the primary genetic component of type 2 diabetes (15). Such a concept fails to explain why most

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IGT, impaired glucose tolerance.

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obese individuals, who of course are insulin resistant, do not develop diabetes. If one accepts that the normal β-cell adjusts its function to compensate for insulin resistance, then one could explain the development of IGT and type 2 diabetes as a failure of β-cell compensation and that this may be the genetic basis for type 2 diabetes. Acceptance of this proposition does not exclude that environmental/acquired factors (e.g., glucose toxicity [16], lipotoxicity [17], and amyloid accumulation in islets [18]) might also be involved.

In this article, previously published work of the author's laboratory is reviewed as is that of other investigators that relates to the questions of whether first-phase insulin release is the earliest detectable defect in β-cell function and whether impaired β-cell function precedes insulin resistance in the pathogenesis of type 2 diabetes.

FIRST-PHASE VERSUS SECOND-PHASE INSULIN RELEASE

During the past 10 years, as part of a multinational collaborative project involving centers in the U.S., Finland, Norway, Greece, and Italy, we have been investigating β-cell function and insulin sensitivity in nondiabetic individuals with and without a first-degree relative with type 2 diabetes (19–21). These individuals were all Caucasian and had either normal or impaired glucose tolerance according to World Health Organization criteria. To evaluate individual phases of insulin release and insulin sensitivity, 3-h hyperglycemic glucose clamps were used. First-phase insulin release was taken as the sum of the increments in plasma insulin over the initial 10 min, and second-phase insulin release was taken as the average plasma insulin level or increment during the last hour of the clamp. Insulin sensitivity was calculated as the glucose infusion rate necessary to maintain the clamp during the last hour divided by the plasma insulin level during that period. The basis for this was the assumption that the glucose infusion rate would depend on the prevailing insulinemia and the responsiveness of tissues to that insulin. Because the glucose infusion rate reflects the sum of the suppression of endogenous glucose release and the stimulation of glucose disposal, it represents whole-body insulin sensitivity. In addition, this approach assumes that the effect of the hyperglycemia per se to suppress endogenous glucose release and to augment glucose disposal is negligible compared with the effects of insulin. Insulin sensitivity assessed with the hyperglycemic clamp has been shown to be highly correlated to that determined with the euglycemic-hyperinsulinemic clamp (22).

To date, we have studied 185 individuals with normal glucose tolerance and 98 people with IGT. Their clinical characteristics are shown in Table 1. Because significant differences were observed between the groups for age, BMI, and waist-to-hip ratio, which are known to affect β-cell function and insulin sensitivity, these factors as well as sex were used as covariates for statistical comparisons of β-cell function and insulin sensitivity.

Figure 1 gives the plasma glucose and insulin levels during the hyperglycemic clamp experiments broken down into four groups: those with normal glucose tolerance with (1) and without (2) a first-degree relative with type 2 diabetes and those having IGT with (3) and without (4) a first-degree relative with type 2 diabetes. It is clear that the hyperglycemic stimulus for insulin secretion was comparable in all groups.

TABLE 1
Clinical characteristics of subjects

	Normal glucose tolerance	Impaired glucose tolerance
n	185	98
Sex (M/F)	63/122	38/60
Age (years)	43 ± 1	49 ± 1*
BMI (kg/m^2)	26.1 ± 0.3	28.0 ± 0.5*
Waist-to-hip ratio	0.82 ± 0.01	0.88 ± 0.01*
Lean body mass (kg)	51.1 ± 0.5	51.2 ± 0.8
Fat mass (kg)	24.5 ± 0.6	27.5 ± 1.0*
HbA_{1c} (%)	5.11 ± 0.04	5.56 ± 0.06*
Fasting plasma glucose (mmol/l)	5.04 ± 0.04	5.49 ± 0.05*
Fasting plasma insulin (pmol/l)	38 (35–40)†	53 (47–61)*†

Data are means ± SE unless noted otherwise. *$P < 0.01$; †95% confidence limits.

As shown in Table 2, both first- and second-phase insulin release were reduced in people with IGT, as was insulin sensitivity. These data therefore do not provide evidence for priority for reductions in first-phase insulin release versus second-phase insulin release or for insulin resistance preceding impaired β-cell function. However, because first-phase insulin release was reduced by ~35% and second-phase insulin release was reduced by ~28%, whereas insulin sensitivity was reduced by ~15%, it appears that the decrement in β-cell function was greater than that in insulin sensitivity.

Table 2 also provides data on differences in the phases of insulin release and insulin sensitivity in individuals with and without a family history of diabetes. As has been previously reported (19–28), there was clear-cut evidence for reduced β-cell function in individuals with a family

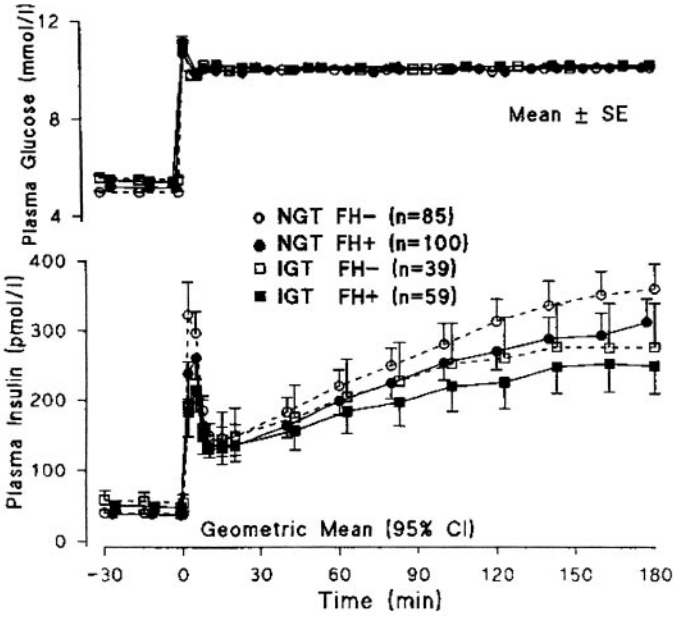

FIG. 1. Plasma glucose and insulin levels during hyperglycemic clamps. Reproduced with permission from Van Haeften et al. (20). FH, family history; NGT, normal glucose tolerance.

TABLE 2
Indexes of insulin secretion and insulin sensitivity in subjects with normal glucose tolerance (NGT) and IGT

	NGT			IGT		
	All	FH^-	FH^+	All	FH^-	FH^+
Insulin secretion						
First-phase (pmol/l)	711 (651–777)	796 (718–883)	647 (562–745)*	467 (398–548)†	449 (359–562)‡	480 (378–609)§
Second-phase (pmol/l)	281 (261–304)	301 (272–334)	266 (239–297)‖	203 (178–233)†	209 (176–249)‡	199 (160–248)§
Insulin sensitivity ($\mu mol \cdot kg$ $LBM^{-1} \cdot min^{-1} \cdot pmol^{-1} \cdot l^{-1}$)	0.236 ± 0.008	0.228 ± 0.011	0.242 ± 0.012	0.202 ± 0.012†	0.179 ± 0.019¶	0.217 ± 0.016

Data for insulin secretion are geometric means (95% CI). Data for insulin sensitivity are means ± SE. *$P < 0.01$; †$P < 0.001$, all IGT vs. all NGT; ‡$P < 0.0001$; §$P < 0.01$, IGT family history $(FH)^+$ vs. NGT FH^+. ‖$P < 0.05$, NGT FH^+ vs. NGT FH^-; ¶$P < 0.02$, IGT FH^- vs. NGT FH^-.

history of diabetes. Both phases of insulin release were reduced: first phase slightly more than second phase (~19 vs. ~12%). It is of note that insulin sensitivity was not reduced in these subjects.

We have not as yet analyzed these data to examine the coincidence of reductions in first- and second-phase insulin release, but in an earlier study of subjects with normal glucose tolerance, differing only in whether they had a first-degree relative with type 2 diabetes (19), we also found that people with a first-degree relative with type 2 diabetes had reduced β-cell function (but no insulin resistance) and that some had reductions in only first-phase insulin release; some had reductions only in second-phase insulin release, whereas others had reductions in both phases of insulin release. We interpret these results to be consistent with genetic heterogeneity for impaired β-cell function.

IMPAIRED β-CELL FUNCTION VERSUS INSULIN RESISTANCE AS THE EARLIEST DEFECT

As alluded to previously, people with IGT already have impaired β-cell function and insulin resistance although the reductions in β-cell function are approximately twice as great as those of insulin sensitivity. As shown in Fig. 2, in which both first- and second-phase insulin release are plotted as a function of insulin sensitivity, for any given degree of insulin resistance, each phase of insulin release is reduced in people with IGT. These data are not compatible with insulin resistance as the primary defect; if that were the case, one would expect to find greater β-cell function for a given degree of insulin resistance.

Analyzing these data further in terms of individuals with and without a first-degree relative with type 2 diabetes (Table 2), we found that those with a first-degree relative with type 2 diabetes were comparably insulin resistant and had a comparable degree of impaired β-cell function for a comparable degree of glucose intolerance as indicated by HbA_{1c} levels (5.59 ± 0.07 and 5.54 ± 0.07%). From these data, one cannot make any inferences regarding time of onset.

However, comparison of individuals with normal glucose tolerance with and without a first-degree relative with type 2 diabetes does provide insight into this issue. As shown in Table 2, individuals with a first-degree relative with type 2 diabetes already have reductions in first- and second-phase insulin release while having no change in insulin sensitivity. This finding strongly suggests that impaired β-cell function precedes insulin resistance in those with a genetic predisposition to develop type 2 diabetes and thus that impaired β-cell function is the primary defect for type 2 diabetes.

It has been argued that studies such as this include individuals who will not get type 2 diabetes. For such an argument to be a valid objection to the conclusions drawn, one would have to hypothesize that those not destined to get type 2 diabetes would have reduced β-cell function and better insulin sensitivity than those destined to get type 2 diabetes. From a common sense point of view, this hypothesis seems highly unlikely and is at variance with the results of studies of monozygotic twins discordant for type 2 diabetes.

Given that the ultimate concordance rate for type 2 diabetes in monozygotic twins is >80%, one can infer that the monozygotic twin with normal glucose tolerance is a true prediabetic subject. There have been four studies of pairs of monozygotic twins in which one still has normal glucose (23–26). In all studies, evidence for impaired β-cell function has been found. In the only study (26) that simultaneously examined insulin sensitivity, insulin sensitivity was found not to be significantly reduced, whereas first-phase insulin release was reduced.

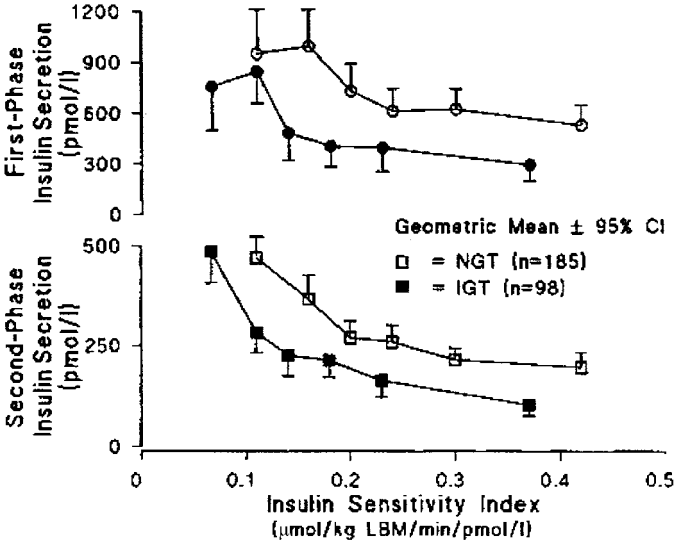

FIG. 2. Relationship between first- and second-phase insulin release and insulin sensitivity in subjects with normal glucose tolerance (NGT) and those with IGT. Reproduced with permission from Van Haeften et al. (20). LBM, lean body mass.

TABLE 3
Partial correlation coefficients determined with multiple linear regression of baseline characteristics and parameters of insulin secretion and insulin sensitivity as estimated during hyperglycemic clamps

	First phase	Second phase	Insulin sensitivity
Family history	−0.13*	−0.14*	0.08
Sex	−0.11	−0.02	−0.002
Age	−0.11	−0.15*	−0.03
Body weight	−0.01	0.02	0.02
Height	−0.02	0.02	0.02
BMI	0.28†	0.41†	−0.44†
Waist-to-hip ratio	−0.02	0.03	−0.14*
Multiple *R*	0.34†	0.43†	0.51†

$n = 283$. *$P < 0.05$, †$P < 0.00001$.

DETERMINANTS OF THE FIRST AND SECOND PHASES OF INSULIN RELEASE AND INSULIN SENSITIVITY

To further assess the genetic influence on β-cell function and insulin sensitivity, we examined the influence of family history of diabetes as well as other factors, such as age, sex, body weight, BMI, and waist-to-hip ratio, using multiple linear regression. As shown in Table 3, first phase and second phase were correlated with family history and BMI, the latter probably reflecting the influence of insulin resistance on β-cell function. First- and second-phase insulin release only differed in that age was negatively correlated with second-phase release. In contrast, insulin sensitivity was not correlated with a family history of diabetes but was with BMI and waist-to-hip ratio. These observations did not provide evidence for a major genetic influence on the insulin resistance associated with type 2 diabetes but do suggest that a major factor is excess body weight and its distribution. Of course, there is evidence that body fat and its distribution are under genetic control (29), but this would not represent a specific diabetes gene.

CONCLUSIONS

Based on the data presented above, a simple working model for the pathogenesis of type 2 diabetes is presented: certain individuals are born with genetically abnormal islets. This abnormality may be a reduced islet cell mass, accelerated apoptosis, susceptibility to amyloid toxicity, and other as yet undiscovered abnormalities. This genetic predisposition ultimately limits the ability to compensate for insulin resistance. Some individuals who remain lean and fit may never develop diabetes or may do so at a very old age because of progressive deterioration in β-cell function. In others who become insulin resistant because of weight gain, physical inactivity, high-fat diets, medications, etc., and are at risk of developing type 2 diabetes, age of onset and severity of diabetes will be determined by the balance between the ability of the β-cell to compensate and the degree of insulin resistance. This schema is consistent with the findings of abnormal β-cell function in individuals at high risk of developing type 2 diabetes on a genetic basis (i.e., the normoglycemic monozygotic twin of a patient with type 2 diabetes) (23–26) and the findings of the U.K. Prospective Diabetes Study (30) and Belfast Diet Study (31) demonstrating an ~50% reduction in β-cell function at diagnosis of type 2 diabetes and subsequent further deterioration without an associated change in insulin sensitivity. Finally, this schema is consistent with therapeutic interventions aimed at preserving β-cell function/insulin secretion and at reducing the burden of insulin resistance.

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