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β-Cell function in type 2 diabetes

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ABSTRACT

Different *in vivo* tests explore different aspects of β-cell function. Because intercorrelation of insulin secretion indices is modest, no single *in vivo* test allows β-cell function to be assessed with accuracy and specificity comparable to insulin sensitivity. Physiologically-based mathematical modeling is necessary to interpret insulin secretory responses in terms of relevant parameters of β-cell function. Models can be used to analyze intravenous glucose tests, but secretory responses to intravenous glucose may be paradoxical in subjects with diabetes. Use of oral glucose (or mixed meal) data may be preferable not only for simplicity but also for physiological interpretation.

While the disposition index focuses on the relationship between insulin secretion and insulin resistance, secretion parameters reflecting the dynamic response to changing glucose levels over a time frame of minutes or hours – such as β-cell glucose sensitivity – are key to explain changes in glucose tolerance and are largely independent of insulin sensitivity.

Pathognomonic of the β-cell defect of type 2 diabetes is a reduced glucose sensitivity, which is accompanied by normal or raised absolute insulin secretion rates – compensatory to the attendant insulin resistance – and impaired incretin-induced potentiation. As β-cell mass is frequently within the range of nondiabetic individuals, these defects are predominantly functional and potentially reversible.

Any intervention, on lifestyle or with drugs, that improves glucose tolerance does so primarily through increased β-cell glucose sensitivity. So far, however, no intervention has proven unequivocally capable of modifying the natural course of β-cell dysfunction.

1. Introduction

The endocrine pancreas is a diffuse organ, made up of roughly one million islets, each endowed with ~1,000 β-cells, for a total weight of ~0.9 g. Despite its small size, the endocrine pancreas has a considerable functional reserve; even simply in terms of stored hormone, pancreatic insulin content has been estimated to range 200–250 units (10-days' worth of supply for a healthy lean adult) [1]. Human islets are highly organized aggregates of β-cells intermingled with α-cells and δ-cells. β-cells represent a higher proportion of total endocrine cells in small than large islets; small islets also have a higher

Abbreviations: OGTT, oral glucose tolerance test; IVGTT, intravenous glucose tolerance test; AIR, acute insulin response to intravenous glucose; AIR_{max}, maximal insulin secretory response; NGT, normal glucose tolerance; IFG, impaired fasting glycemia; IGT, impaired glucose tolerance; T2D, type 2 diabetes; HOMA-B, homeostatic model assessment-insulin secretion; S_I, insulin sensitivity index derived from minimal-model analysis of the IVGTT; DI, disposition index; GLP-1, glucagon-like peptide-1; FFA, free fatty acids; DPP-4, dipeptidyl-peptidase-4; PPAR-γ, peroxisome proliferator-activated receptor γ.

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insulin content and are in closer contact with blood vessels, thereby representing a functionally distinct subpopulation [2]. Within human islets, β-cells form a sparsely connected network, with synchrony detectable only between small cell clusters [3]. Blood flow through the islet appears to proceed in the direction β → α → δ [3], thereby exposing α-cells to the paracrine effect of insulin rather than β-cells to any intraislet action of glucagon.

Functionally, β-cells are the most sophisticated of endocrine cells. Their main product, insulin, must be supplied to the body tissues in amounts and time-dynamics apt to maintain plasma glucose within a narrow concentration range on a minute-by-minute basis. In fact, insulin output must cope with acute challenges – *i.e.*, size, composition and appearance rate of meals – as well as adapting to long-term settings, such as changes in target tissue sensitivity to insulin. In comparison, insulin action, if equally complex at the cellular level, is a relatively stable function in any given individual. In fact, when measured *in vivo* by a direct technique (the euglycemic hyperinsulinemic clamp), insulin sensitivity has been shown to vary by 30–80% during 24 hours of free living [4]. With physiological or pharmacological intervention, in most cases insulin sensitivity can be at best doubled [5], whilst insulin secretion can vary many fold in the same person in a matter of minutes, as occurs with a large mixed meal, or over years, as happens with weight gain. For example, it has been calculated that a lean, insulin sensitive adult may need as little as 0.5 units of insulin to dispose of an oral load of 75 g of glucose over 2 hours, while an obese, insulin resistant, glucose intolerant subject may require 45 units to perform the same task, a ~100-fold span [6]. Equally striking is the case of bariatric surgery: in morbidly obese, nondiabetic subjects who had lost 50 kg of bodyweight following the operation, insulin output dropped by 60% – from 65 to 25 units per day – in concomitance with normalization of insulin resistance [7].

The immediate consequence of such extensive physiological flexibility is that no single *in vivo* test (or, for that matter, even *in vitro* test) can capture all the major facets of β-cell function. It follows that nailing the β-cell defect of type 2 diabetes – universally recognized as the *sine qua non* of the disease [8] – depends on the method of testing employed. Therefore, we shall first briefly re-assess the value and significance of the tests currently employed to measure β-cell function *in vivo* and the physiologic and pathophysiologic inferences that have been based on these tests [9–11], and then highlight the problems with the β-cell in diabetes.

2. Testing β-cell function *in vivo*

The majority of the published data on β-cell function are expressed as plasma insulin levels, despite that the insulin assay still eludes standardization [12]. More importantly, circulating insulin concentrations are dependent upon β-cell insulin release through insulin distribution and clearance [13]. In general, whole-body insulin clearance occurs mostly *via* hepatic degradation (the kidneys contributing ~20%), and is regulated by the insulin concentration itself through a saturable process. Thus, hepatic and renal insufficiency are associated with a degree of hyperinsulinemia resulting from reduced organ clearance [13]. In the liver, insulin degradation is partly receptor-mediated and is coupled with insulin action; therefore, insulin resistant subjects typically show decreased insulin clearance [14]. Deconvolution analysis (initially applied to insulin [15]) of plasma C-peptide concentrations [16] using a standard plasma C-peptide kinetic model [17] has made it possible to reconstruct insulin secretory rates from peripheral C-peptide concentrations. The method is based on the fact that insulin and C-peptide are released by β-cells in equimolar amounts but only the former undergoes liver extraction. As a consequence, the kinetics of C-peptide in peripheral plasma reflect the kinetics of pancreatic insulin release and can be used to calculate C-peptide secretion rates from plasma C-peptide concentrations.

Fasting plasma insulin concentrations are a poor index of β-cell function for two reasons. Firstly, fasting plasma insulin does not accurately reflect pancreatic secretion, as discussed above. Secondly, fasting insulin levels do not take fasting glucose concentrations into account. In fact, fasting insulin secretion bears a complex relation to glucose levels, rising in individuals with impaired glucose tolerance (IGT), peaking in mild diabetes, and then gradually falling off as hyperglycemia worsens [18]. The HOMA-B index, based on the ratio of fasting insulin to fasting glucose, suffers from major limitations despite being based on a sophisticated system model [19]. By way of example, in 18 obese subjects with impaired glucose tolerance (IGT) with a mean fasting glucose of 5.77 mmol/L and a fasting insulin of 84 pmol/L, the HOMA2 calculator (freely available on line at http://www.dtu.ox.ac.uk/homacalculator/) yields a mean percent β-cell function of 98% of 'normal', whereas β-cell glucose sensitivity (see below for the definition of this parameter) is actually reduced by 50% as compared to 21 weight-matched subjects with normal glucose tolerance (NGT) (personal data).

Glucose administered as an intravenous bolus (as in the intravenous glucose tolerance test, IVGTT) triggers a multiphasic secretory response, in which secondary peaks, in phase with corresponding plasma glucose peaks, can often be discerned [15]. For this reason, only the first burst of insulin release (also termed acute insulin response, AIR) is usually considered. Quantitation of AIR has varied from the sum of insulin concentration values at multiple times following glucose injection [20] to the increments above baseline of plasma insulin values at 2 to10 min [21]. Only a few studies have reconstructed insulin secretion rates during an IVGTT. With the hyperglycemic clamp technique, a biphasic insulin response is usually clearly detectable, with a first phase, which is extinguished within ~10 min, followed by a second phase of progressively rising insulin release. The hyperglycemic clamp has been used to achieve glycemic plateau's from 7.2 [22] to 16.7 mmol/l [23], from different fasting glucose levels, and for variable periods of time, thereby eliciting very different biphasic patterns. Moreover, when two or more glycemic steps are applied in succession, there is a progressive loss of AIR, whereas second-phase insulin secretion is unaffected [22].

Graded intravenous glucose infusions [24], and variations thereof such as ascending/descending glucose ramps [25], have been used to create dose-response relationships

between plasma glucose concentration and insulin secretion rate. Ward and colleagues [26] have pioneered the use of intravenous arginine boluses superimposed on progressively higher, short hyperglycemic plateau's to calculate the slope of arginine-induced AIR *vs* plasma glucose (termed glucose potentiation slope), and to estimate a maximal (or near-maximal) response (AIR_{max}). Of note, this slope is conceptually different from the slope one calculates from graded glucose infusions, which investigate mostly second-phase, or slow, insulin responses.

It is important to point out that, after years of painstaking research the physiological interpretation of AIR (or AIR_{max}) is still uncertain. Single-cell electrophysiological studies have shown that acute exposure to high glucose enhances electrical activity synchronously with spikes in cytosolic calcium concentrations, which parallel insulin release both in terms of glucose-dependency and time-course [27]. Calcium accumulation is necessary to promote exocytosis (by fusing mature secretory granules with the plasma membrane). However, morphometric studies have shown that the β-cell harbors different populations of secretory granules, in different stages of maturation and in variable spatial array between the trans-Golgi and the plasma membrane, constituting a chain of secretory pools in dynamic exchange with one another [28]. Whilst only a few of the readily releasable granules are necessary to account for the amount of insulin released in AIR, AIR itself is not fixed, *i.e.*, it increases with progressively larger boluses and can be further augmented by other hormones (*e.g.*, GLP-1 [29]).

Administration of glucose (or a mixed meal) by mouth is generally reputed to be a less specific test of β-cell function than intravenous glucose despite its obvious physiological superiority. The reason lies with the fact that other secretagogues (nutrients and gut hormones) concur with glucose to stimulate the β-cell; in addition, the levels of the stimuli change continually with time. Whether and how the seemingly constitutive biphasic β-cell response to acute glucose stimulation contributes to the time-course of insulin secretion in response to oral glucose cannot be resolved. A popular index of acute insulin response to oral glucose is the insulinogenic index, or the insulin-to-glucose ratio at some early time following glucose (or mixed meal) ingestion. Other indices derived from an OGTT are the ratio of insulin-to-glucose area under the curve or the respective increments above baseline. These empirical indices all reflect the need to adjust insulin secretion for the concomitant glucose concentration.

When oral glucose is superimposed on a hyperglycemic plateau established with intravenous glucose, the step-up in insulin secretion rate is a measure of the incretin effect [30]. Alternatively, the plasma glucose response to oral glucose is matched by a variable intravenous glucose infusion, and the incretin effect is measured as the difference in the respective insulin responses [31] (Fig. 1).

3. Intercorrelation of *in vivo* tests of insulin secretion

Correlation between different *in vivo* tests of insulin secretion is generally unsatisfactory. For example, in 147 subjects with normal glucose tolerance (NGT) and 46 patients with type 2 diabetes (T2D) receiving both an OGTT and an IVGTT [32], AIR was virtually absent in the T2D patients while their secretory response to oral glucose was rather robust, although reduced compared to the NGT group (Fig. 2). These data strongly suggest that the IVGTT may not be the ideal test to assess β-cell function in diabetes, and that AIR, probably the most common empirical index of insulin secretion (and one that has generated valuable information about the progression of IGT to diabetes [33]), overestimates the degree of β-cell incompetence in diabetes and, consequently, underestimates the extent to which β-cell function could be improved by intervention.

4. Mathematical modeling of β-cell function

Because of the difficulties mentioned above, mathematical models have become almost indispensable tools to describe complex functions; many have been developed to interpret insulin secretory responses since the early studies on β-cell function in the isolated perfused rat pancreas and in man [34–42]. These models, particularly those by Grodsky and Licko [35,43] and Cerasi and colleagues [36], have established the fundamental mathematical constructs necessary to describe β-cell function. These constructs are relatively straightforward. Firstly, insulin secretion rates follow plasma glucose concentrations proportionally, *i.e.*, according to a dose-response function. For example, when the insulin secretion rates measured during an OGTT (Fig. 2) are plotted against the concomitant plasma glucose levels, there emerges a quasi-linear dose-response function, whereby each increment in glucose is associated with an increment in secretion: the average slope of this function is a measure of β-cell glucose sensitivity (Fig. 3). Secondly, the isolated perfused pancreas or cultured β-cells respond not only to the level of glucose but also appear to be sensitive to the rate of change of glucose levels (rate sensitivity). The existence of this 'derivative' response mode *in vivo* is best exemplified by subjects undergoing gastric bypass surgery. After the operation, which greatly reduces stomach size and bypasses the pylorus, gastric emptying is accelerated, whereby plasma glucose excursions after a meal show an early peak followed by a rapid fall (Fig. 4). The concomitant plasma insulin concentrations and insulin secretion rates parallel the plasma glucose time-course. In this situation, the model-derived parameter quantifying β-cell rate sensitivity increases 3 fold (from 5.2 to 15 $nmol \cdot m^{-2}$) [44]. Thirdly, potentiation of glucose-induced insulin release is a well characterized feature of β-cell function *in vitro* and *in vivo* [36,43,45]. Its operation during an OGTT is demonstrated in Fig. 5, where the plasma insulin values at sequential times after glucose ingestion are plotted against the concomitant plasma glucose values. In both NGT and IGT individuals, it can be seen that insulin levels at similar plasma glucose levels are higher at later than earlier times during the OGTT. Another clear manifestation of potentiation occurs during a hyperglycemic clamp, where after the initial burst insulin release rises continually despite constant glucose levels [45]. Finally, the higher insulin release during oral than intravenous glucose administration at matched plasma glucose concentrations (Fig. 1) reflects, and in fact measures, incretin-induced potentiation.

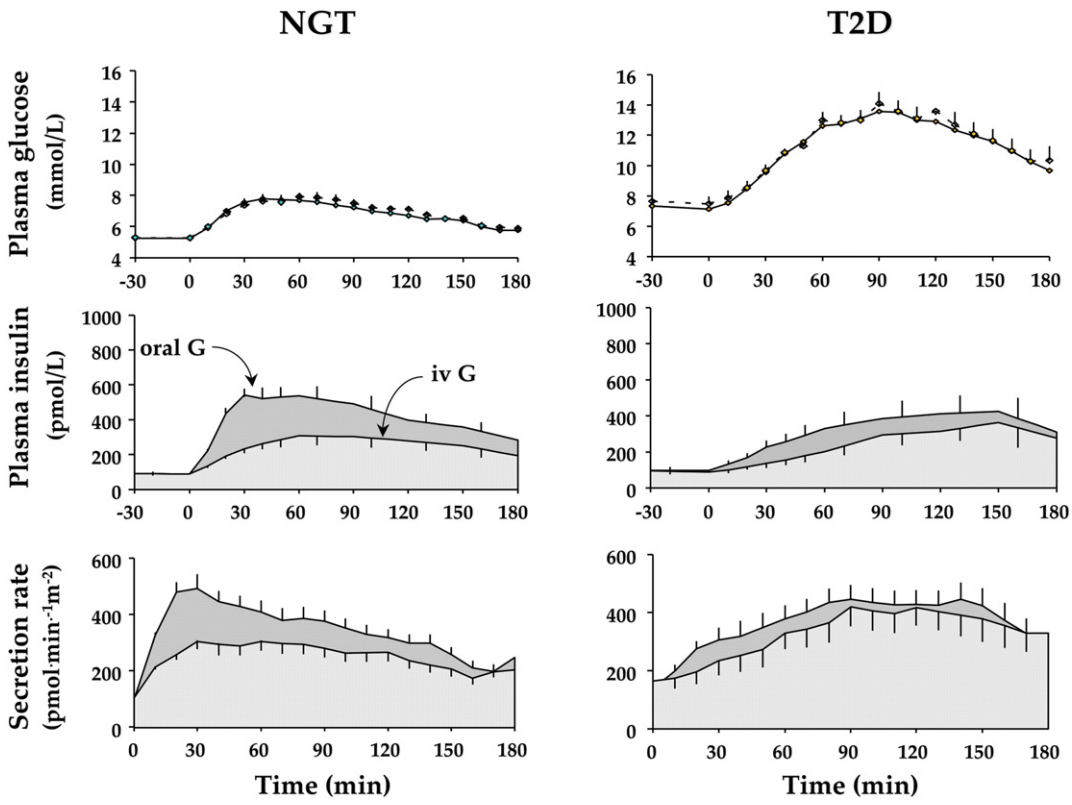

Fig. 1 – Plasma glucose and insulin concentrations and insulin secretion rates following oral glucose tolerance administration (oral G) and isoglycemic intravenous glucose infusions (iv G) in subjects with normal glucose tolerance (NGT) and type 2 diabetes (T2D). Data are mean ± SEM. Redrawn from ref. [31].

It must be observed that despite some differences in model-building strategies, the information generated by the application of different mathematical models to β-cell function in diabetes appears to be essentially concordant, as discussed below.

5. Relationship between insulin secretion and insulin resistance

The relationship between insulin resistance and β-cell function is of great interest because of the physiological

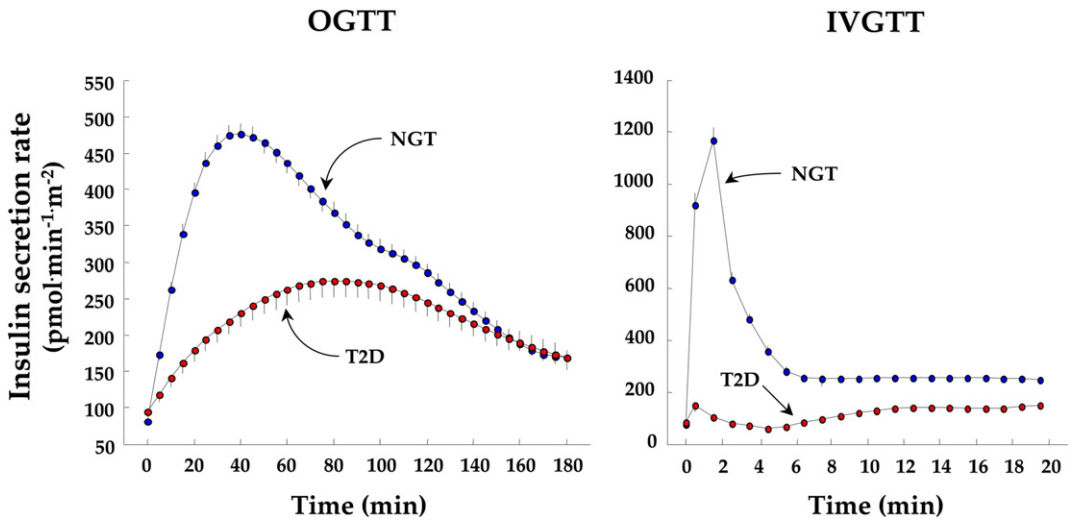

Fig. 2 – Insulin secretion rates during a standard OGTT (75 g) and a standard IVGTT (0.33 g/kg) in subjects with normal glucose tolerance (NGT) and type 2 diabetes (T2D). Data are mean ± SEM. Redrawn from ref. [32].

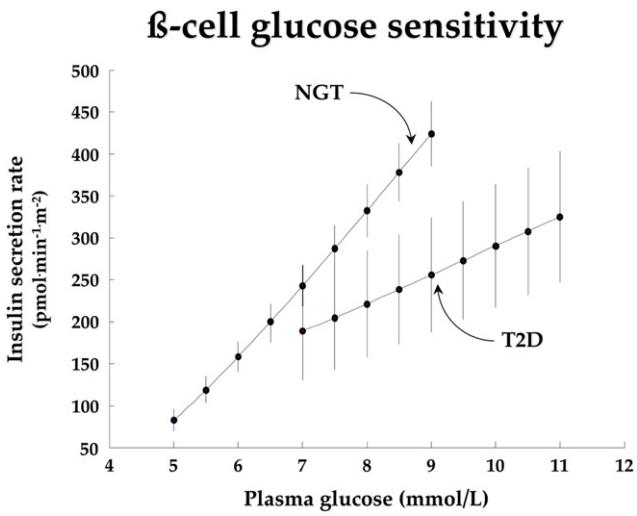

Fig. 3 – The insulin secretion rate data in Fig. 2, left panel, are plotted against the concomitant plasma glucose concentrations measured during the OGTT. Data are mean ± SEM.

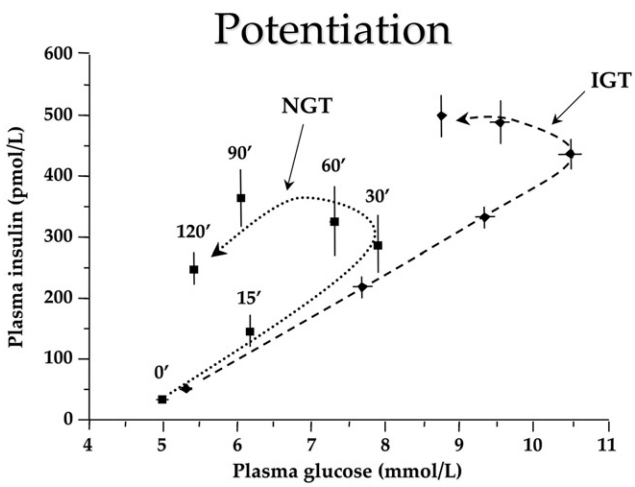

Fig. 5 – Plasma insulin are plotted against the concomitant plasma glucose concentrations at various timed during an OGTT in subjects with normal (NGT) or impaired glucose tolerance (IGT). Data are mean ± SEM. Redrawn from ref. [55].

feedback linking the two functions *in vivo*. The obvious example of the operation of such a feedback is obesity: in nondiabetic subjects, both basal insulin secretion rate (ISR) and total insulin release during an OGTT increase linearly with the BMI. The current interpretation of this relationship is that the insulin resistance of obese individuals signals back to the β-cell to enhance its insulin output in order to maintain normal glucose tolerance. Thus, a logical evolution of this notion has been to formally relate insulin secretion to insulin action. Kahn and co-workers [46] have pioneered the concept that a hyperbolic relationship exists between β-cell function and insulin sensitivity, and that constancy of their product across a wide range of β-cell responses and insulin sensitivity is key to maintaining glucose tolerance.[1] Using data obtained from an IVGTT-minimal model in a small group of young healthy subjects, the plots of the insulin sensitivity index (S_I) against (a) fasting plasma insulin, (b) AIR, (c) the potentiation slope or (d) AIR_{max} (derived from Ward's protocol [26]) could all be adequately fit with log-log functions with exponent close to −1 (ranging from −0.84 to −1.19). Thus, a disposition index (DI, *i.e.*, the product of insulin sensitivity and insulin secretory response) was recommended as a composite parameter quantifying glucose disposition *in vivo*. The hyperbola paradigm has become quite popular because it hinges upon the intuitive concept that the β-cell must compensate for the presence of insulin resistance [47]. In longitudinal analyses of glucose tolerance in Pima Indians [48], the normal 'compensation line' (in the log-log plot of AIR against S_I) was interpreted as regressing towards the origin of the axes as glucose tolerance deteriorated through IGT to overt T2D. An oral DI has been developed from the analysis of OGTT or mixed meal data, thereby extending the rationale to more physiologic and easier tests [49].

The hyperbola approach is, however, problematic. Firstly, calculating a DI is only valid if the fitting function is an rectangular hyperbola (linearized to a straight line of slope equal to −1 in log-log plots such as in Fig. 6). In contrast, we

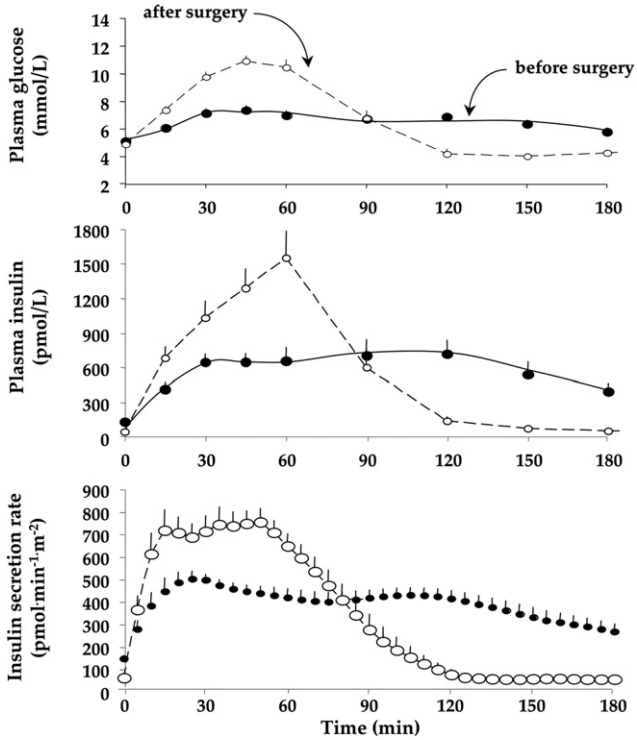

Fig. 4 – Plasma glucose and insulin concentrations and insulin secretion rates during a mixed meal in nondiabetic subjects before (*filled symbols*) and 1 year after Roux-en-Y gastric bypass surgery (*empty symbols*). Data are mean ± SEM. Redrawn from ref. [44].

[1] A rectangular hyperbolic function, $\beta = a.\sigma^{-1}$, where β is insulin secretion and σ is insulin sensitivity, is such that each of its points can be described by a single constant parameter, called disposition index (DI = ß.σ). As DI decreases, curves regress towards the axis origin and glucose tolerance worsens. Hyperbolas can be linearized by log-log transformation (ln[ß] = ln[a] − ln[σ]).

have shown [50] that the shape of the relationship between insulin sensitivity and insulin secretion depends not only on the quality of experimental data but also on the metric employed to index insulin sensitivity and secretion. While in general a non-linear fit is statistically superior to a linear fit, and, in most cases, the best fit is indeed a log-log function, the exponent can be significantly different from −1 (ranging from −0.7 to −1.8, with *r* values between 0.46–0.75) even just in subjects with NGT. Secondly, a defective compensation implies that insulin secretion is adequate when insulin sensitivity is normal but begins to fail as insulin resistance ensues. In this case, the slope of the log-log relationship is flatter, as schematized in Fig. 6. On the other hand, if secretion is lower at any level of insulin sensitivity – as the parallel shift towards the axis origin implies – then the implication is that the underlying problem is an intrinsic β-cell defect and not an impaired compensation.

On the other hand, the hyperbola paradigm has proven useful in focusing attention to the fact that there are modes of β-cell response that are coupled to insulin action in the intact organism. However, analysis of multiple datasets from cross-sectional [51–55] and longitudinal studies [56–58] has demonstrated the β-cell does not respond to insulin resistance by upregulating *all* its functions. In particular, indices of absolute insulin release, such as the fasting insulin secretion rate and the total insulin output during an OGTT or a mixed meal, are reciprocally related to insulin sensitivity in NGT, IGT, and T2D cohorts. This confirms that insulin resistance feeds back to the β-cell by raising its secretory tone (or setpoint). This *chronic* adaptation is likely mediated by even minor increments in plasma glucose concentrations (such as occur in obese NGT individuals) as well as, possibly, by other factors such as raised free fatty acids (FFA) [59]. In contrast, indices of dynamic β-cell responsiveness, such as glucose sensitivity and rate sensitivity, which reflect the *acute* response to changing glucose levels over a time frame of minutes or hours, bear only a loose relation to insulin sensitivity. This result is in keeping with the interpretation of studies using the graded intravenous glucose infusions protocol [60]. AIR (intravenous glucose) and the insulinogenic index (OGTT), which reflect both the β-cell setpoint and some dynamic aspect of its secretory response, are hybrid indices of function and as such they will be variably related to insulin sensitivity across states of glucose intolerance and over time [50].

By multivariate analysis of a large NGT cohort [57], the contribution of insulin sensitivity and dynamic β-cell response to the glucose levels measured during an OGTT has been reconstructed as shown in Fig. 7: early glycemia are influenced by glucose sensitivity and rate sensitivity, later glycemia by insulin sensitivity and potentiation.

6. β-Cell function in diabetes

The conceptual framework delineated in the preceding paragraphs makes it possible to distill the large amount of published information on β-cell dysfunction down to a few basic facts. In overt type 2 diabetes, insulin resistance is associated with the following abnormalities of β-cell function:

a) Fasting insulin secretion and total stimulated insulin output are increased as a result of the prevailing hyperglycemia, and are correlated with insulin resistance in a positive fashion; in time, as hyperglycemia worsens total insulin output begins to decline;
b) Glucose sensitivity is markedly impaired, typical values being 1/3 to 1/5 of those of NGT subjects (Fig. 3); this parameter is the single best descriptor of β-cell incompetence as a continuum across glucose tolerance state from NGT to IGT to T2D (Fig. 8);
c) Rate sensitivity also is reduced, reflecting the inability to promptly respond to glucose increments (Fig. 2);
d) The incretin effect is generally reduced (Fig. 1). In particular, recent work [61] has made it possible to separate *glucose-mediated* from *incretin-mediated* potentiation by combined analysis of oral and intravenous isoglycemic protocols. The results show that, while glucose potentiation is actually augmented in T2D compared to NGT (due to

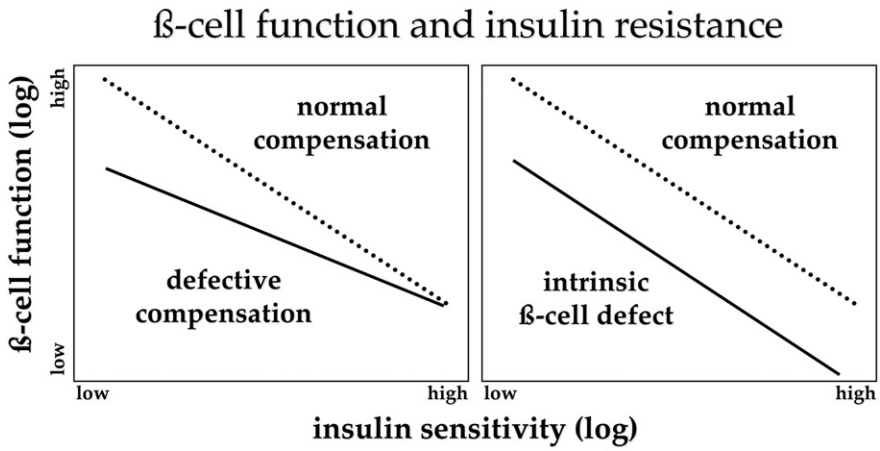

Fig. 6 – Theoretical hyperbolic relationship ($\beta = a.\sigma^{-1}$) between β-cell function (β) and insulin sensitivity (σ). The function is linearized by a log-log transformation (log[β] = log[a] – log[σ]). As hyperbolas differ only in intercept, each point (=subject) on the dotted lines can be described by a single parameter, called disposition index (DI = a = σ.β). See text for interpretation.

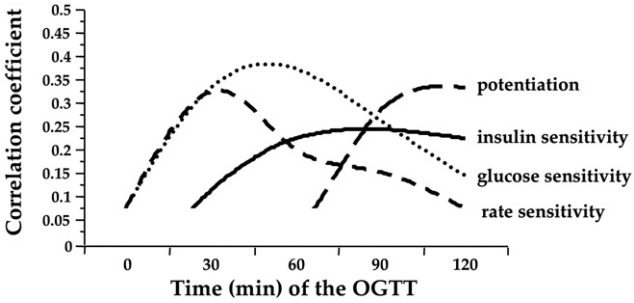

Fig. 7 – Correlation coefficients between the glucose concentration at various times during the OGTT and model-derived parameters of β-cell function (glucose sensitivity, rate sensitivity, and potentiation) and insulin sensitivity. The lines join the corresponding values of correlation coefficients obtained from multiple regression models. Redrawn from ref. [57].

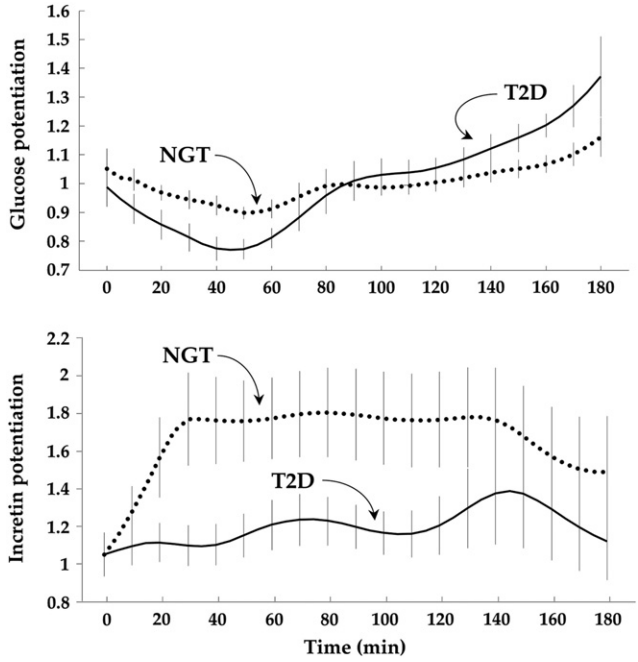

Fig. 9 – Time-course of glucose potentiation and incretin potentiation from the combined modeling analysis of OGTT and isoglycemic glucose infusions. Data are mean ± SEM. Redrawn from ref. [98].

the hyperglycemia), incretin potentiation is severely compromised (Fig. 9). Of interest in this regard are recent findings documenting that the secretory response of GLP-1 – the main incretin hormone – is quite variable in T2D, ranging from reduced to normal, and is poorly correlated with the extent of the incretin defect [61]. Thus, other factors, hormonal or neural, must contribute to the incretin defect of T2D. Among the hormonal factors, glucose-dependent insulinotropic polypeptide (GIP) causes little potentiation of insulin release in T2D despite raised GIP responses to oral stimuli [62].

In addition to these defects, the autocrine effect of insulin to stimulate its own release has been shown to be significantly reduced in insulin resistant states [63]. Finally, and most importantly, impaired β-cell glucose sensitivity is a powerful predictor of progression to dysglycemia/T2D in subjects with NGT independently of insulin resistance and on top of the classical phenotypic indicators (age, adiposity, familial diabetes) [56,57]. In these multivariate predictive models, insulin secretion is a positive antecedent of deteriorating glucose tolerance, thereby emphasizing the contrasting value of *absolute* insulin release *viz.* the *dynamics* of insulin response.

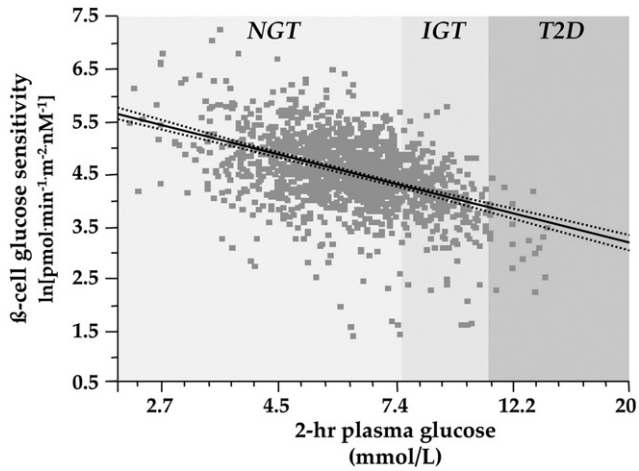

Fig. 8 – Reciprocal association between β-cell glucose sensitivity and the 2-hour plasma glucose concentration on the OGTT in 1480 individuals spanning the range from normal glucose tolerance (NGT) to impaired glucose tolerance (IGT) to overt type 2 diabetes (T2D). The full line is the best fit (and its 95% confidence intervals, dotted lines) adjusted for sex, age, and body mass index (BMI). Data from refs. [54,57].

7. β-Cell dysfunction *vs* reduced β-cell mass

It is a long-held notion that β-cell mass is decreased in patients with T2D. In autopsy series, a reduction in β-cell relative volume [64,65] or mass [1] has been reported in T2D; other morphological and histochemical evidence documents structural disarray and amyloid infiltration in human diabetic islets [66]. Moreover, the vast majority of gene variants that genome-wide scans have associated with T2D are related to some aspect of β-cell function, growth or survival [67–69], and relatively few have involved insulin action/signaling. As a consequence, the etiologic conundrum of T2D includes a 'mass' problem, presenting early in the course of diabetes, possibly detectable *in vivo* (with the development of direct imaging techniques), and therapeutically 'drug-able' (using trophic factors or stem cells). However, the best autopsy data show a very large variability in islet mass, and a wide overlap between nondiabetic and T2D subjects [1], whereas *in vivo* testing shows an almost complete separation of β-cell glucose sensitivity between NGT subjects and patients with overt T2D (Fig. 10). The following circumstances should also be considered: (a) autopsy specimens are usually from sick patients of advanced age whose glucose intolerance is uncertain in degree (subjects with impaired fasting glycemia (IFG) might be diabetic on the OGTT) as well as duration; (b) pancreatic amyloidosis could be the consequence rather than the cause of hyperglycemia [70,71]; (c) when islets obtained from donors with T2D are studied under 'healthy' culture conditions, they show defective responses to glucose [72]; (d) together with insulin resistance, β-cell glucose insensitivity independently predicts and antecedes the emergence of dysglycemia in young subjects with normal glucose tolerance [56,57], that is, at a time when β-cell mass would be mostly normal; (e) intensified insulin therapy, incretin mimetics (GLP-1), or, indeed, any treatment resulting in amelioration of glycemic control is associated with partial reversal of β-cell dysfunction, and (f) bariatric surgery is followed by long-lasting resolution of diabetes in a high proportion of T2D patients, in some cases with full recovery of β-cell glucose sensitivity. Because in human adults β-cell regeneration appears to occur at a very low rate (if at all), changes in β-cell mass can hardly explain recovery of function. It follows that β-cell mass deficit alone is unlikely to be the cause of most cases of diabetes, whereas β-cell dysfunction theoretically could be the sole mover.

All in all, the available evidence can be logically construed as follows. β-cell dysfunction is sufficient to cause hyperglycemia; reduced β-cell mass is not necessary but, if severe, can be sufficient and may or may not be associated with dysfunctional β-cells. In a time-scale of months or years, insulin resistance is a factor that modulates β-cell secretory capacity (or setpoint) in part at least by driving β-cell mass expansion; the impact of obesity is, at least in part, mediated by insulin resistance. Anecdotal reports of incretin hypersecretion and islet proliferation ("nesidioblastosis") following bariatric surgery provide an additional perspective on the regulation of β-cell mass [73]. If properly done and interpreted, clinical testing can differentiate β-cell capacity from β-cell glucose sensitivity, but cannot ascribe either to changes in mass *vs* function. However, evidence from longitudinal and intervention studies suggests dominance of β-cell dysfunction in the pathogenesis of T2D.

8. Impact of intervention on β-cell dysfunction

Information on the effects of treatment on β-cell function is plentiful but also, not surprisingly, heterogeneous on account of the variety of clinical tests used, the phenotype of the T2D patients investigated, and the clinical circumstances (dose, duration of treatment, comorbidities, etc.). Nonetheless, a few well established conclusions can be made with reference to the paradigm of β-cell function outlined in the preceding sections. Whenever an intervention – be it lifestyle

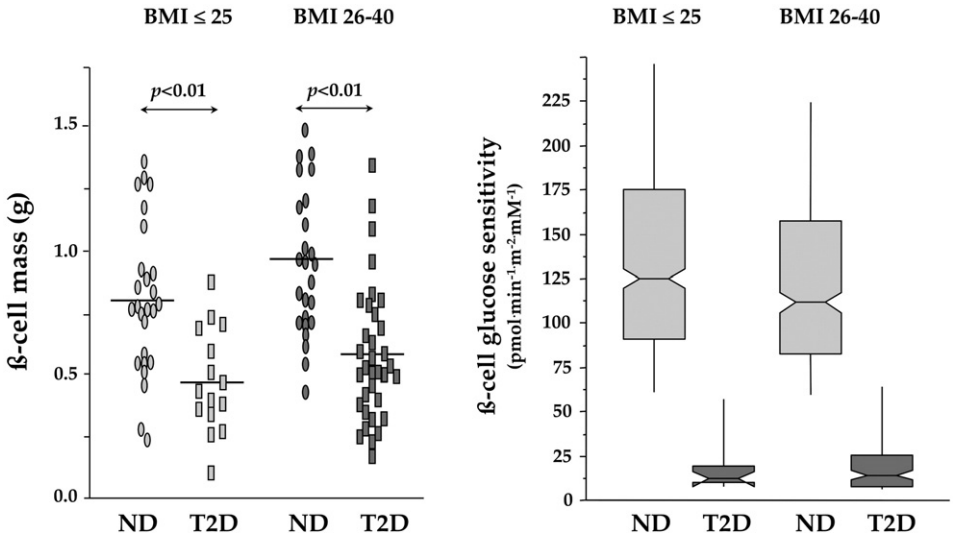

Fig. 10 – *Left panel* – β-cell mass in lean (BMI ≤25 kg/m^2) or obese (BMI 26–40 kg/m^2) nondiabetic (ND) and diabetic (T2D) subjects (*post mortem* specimens, data from ref. [64]). *Right panel* – β-cell glucose sensitivity in lean or obese nondiabetic (n = 1018) and diabetic subjects (n = 106). Unpublished data.

modification [74], glucose-lowering drug therapy with metformin [75], sulfonylureas [75], glinides [76], thiazolidinediones [75], GLP-1 receptor agonists [77], DPP-4 inhibitors [78], sodium-glucose cotransporter-2 inhibitors [79], insulin [80], restrictive [81] or malabsorptive bariatric surgery [82] – results in a reduction in plasma glucose concentrations, the following changes can be detected from the data: (a) fasting insulin secretion rate and total insulin output in response to oral glucose or a mixed meal are reduced, and (b) β-cell glucose sensitivity – as the mean slope of the relationship between insulin secretion and plasma glucose – is improved. With improved glycemia, AIR (iv glucose bolus) and 1st- and 2nd-phase insulin response (hyperglycemic clamp) also are increased.

The reduction in absolute insulin release is explained by the fact that the primary stimulus for insulin secretion is the plasma glucose concentration under virtually all circumstances. Therefore, gauging β-cell function from plasma insulin levels (or secretion rates) out of context of the concomitant plasma glucose levels can be misleading. Glucose sensitivity is the most 'sensitive' index of β-cell function, capable of detecting smaller changes than other tests along a continuum (Fig. 8). Rate sensitivity can also be demonstrated to improve when treatment results in more rapid insulin responses (as with nateglinide [76] or gastric bypass surgery [81]).

An important point is that, according to available evidence in no case do these improvements in β-cell function appear to impact on the natural history of the β-cell dysfunction of T2D. In fact, in most cases β-cell dysfunction relapses (and glycemic control worsens) upon discontinuing treatment. This is the case even with incretin mimetics (GLP-1 receptor agonists [83] and DPP-4 inhibitors [84]) notwithstanding that these molecules induce clear β-cell proliferation in rodent models [85]. One possible exception is the thiazolidinediones, for which the evidence for a direct effect on β-cell function in T2D is somewhat stronger [75,86–88]: in fact, human β-cells express PPAR-γ receptors [89,90] and in rodent models thiazolidinediones lower islet fat at the same time that they restore β-cell function [91]. *In vivo* proof of an unequivocally direct effect of a drug on β-cell dysfunction requires an equipoise against another drug inducing the same degree of glycemic control, and evidence of some persistence of effect following discontinuation.

Also of note is the accumulating evidence that the incretin defect of T2D is only partially explained by GLP-1 [92], and cannot be detectably changed by treatment of the hyperglycemia, whether by DPP-4 inhibitors [78] or metformin [93]. These observations have led to the notion that loss of incretin effect is a specific characteristic of T2D [94].

Intriguing new avenues of research stem from studies of intraislet cross-talk between β-cells and endothelial cells, which point at the regulation of blood and nutrient supply and the structural disarray of islets [95] as factors in the genesis of β-cell dysfunction in T2D. Also, recent evidence indicates that insulin resistance itself affects the ratio of β-cells to α-cells [96] by promoting a relative preponderance of α-cells over β-cells, possibly through a process of dedifferentiation and subsequent redifferentiation. The overarching picture that emerges is one where even in advanced T2D many β-cells are alive but stunned or disguised, and therefore amenable to being revitalized by intervention [97].

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Disclosure of interest

The authors have nothing to disclose in relation to the contents of this article.

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