HORMONE RESEARCH

Minimal Model: Perspective from 2005

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Key Words
Insulin resistance · Insulin secretion · Genetics · Disposition index · Modelling

Abstract
The minimal model was proposed over 25 years ago. Despite (or because of) its simplicity it continues to be used today – both as a clinical tool and an approach to understanding the composite effects of insulin secretion and insulin sensitivity on glucose tolerance and risk for type 2 diabetes mellitus. The original assumptions of the model have led to an understanding of the kinetics of insulin in vivo, as well as the relative importance of β-cell compensatory failure in the pathogenesis of diabetes. The disposition index (DI), a parameter emerging from the model, represents the ability of the pancreatic islets to compensate for insulin resistance. There is evidence that a locus on chromosome 11 codes for the DI, which has a significant heritability and can predict type 2 diabetes better than any known genetic locus. Even today, the model continues to be a subject of scientific discovery and discourse.

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Origin of the Minimal Model

Mathematical modelling of homeostatic systems has long held great promise to explain the behaviour of closed-loop physiological systems. While modelling has been ac-cepted in cardiovascular and respiratory control [1, 2], the acceptance of models to describe blood glucose regulation was more controversial. Early models were based upon differential equation representations of the dynamic relationships between glucose and insulin, and varied from extremely simple [3] to extremely complex [4]. However, the impact of modelling on the diagnosis and treatment of diabetes mellitus was limited. One reason for the lack of acceptance was the unfamiliarity of many endocrinologists with the process of using mathematical or computer representations to describe closed-loop feedback systems. Additional problems arose from the inherently non-linear nature of the function of the organs that play prominent roles in regulation of the blood glucose concentration.

Modelling the pancreatic islets was a particularly difficult problem. The β-cell is a complex cell demonstrating biphasic insulin secretion, with a response that is altered by previous history of stimulation and a non-linear dose-response curve. These complex characteristics of the β-cells are not amenable to simple representation in mathematical terms [5]. However, it proved to be possible to exploit mathematical modelling and gain substantial information regarding blood glucose regulation while avoiding the hurdles inherent in describing β-cell function in mathematical terms.

To do this we exploited the intravenous glucose tolerance test (IVGTT). We modified the test by making frequent measurements of plasma glucose and insulin following glucose injection – thus revealing the complex dynamic relationship between plasma glucose and insulin.
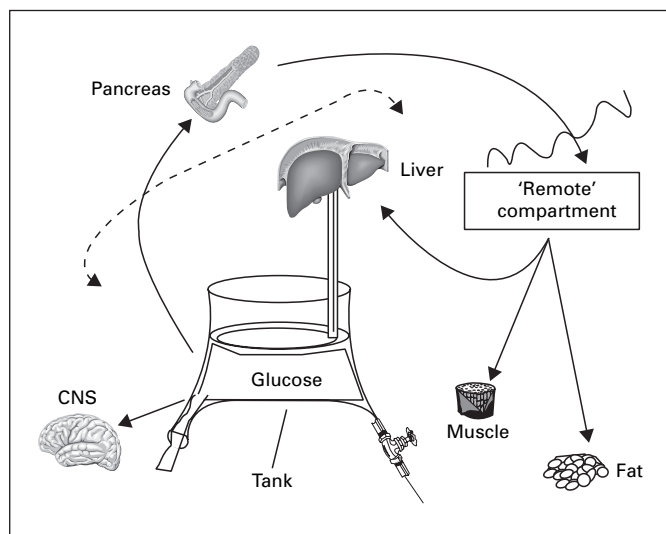
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Fig. 1. Closed-loop relationship between glucose, insulin secretion and insulin action. 'Tank' represents blood glucose in extracellular fluid. The level of glucose (height of fluid) is the balance between the rate of production (flux from liver) and rate of utilization (drainage from tank). After meals, the level of glucose increases (i.e. the height in the tank rises) eliciting an insulin secretory response. Insulin crosses the endothelial barrier (represented by the wavy line), increases glucose uptake by muscle and suppresses lipolysis from adipose tissue, which in turns reduces liver glucose production. To simplify modelling, only the extrapancreatic tissues are represented (indicated by the dotted arrow), including the effects of insulin and glucose per se on net glucose utilization (i.e. production by liver minus uptake by the central nervous system and muscle) [6].

$$\frac{dG}{dt} = -\left\{ S_G + X(t) \right\} * G$$

$$\frac{dX}{dt} = p_2 * I(t) - p_3 * X(t)$$

$$S_I = \frac{p_3}{p_2}$$

$$\text{Glucose restoration rate} = -\left\{ \text{Glucose effectiveness} + \text{Remote insulin} \right\} * G$$

$$\text{Increase in remote insulin} = p_2 * \text{Plasma insulin} - p_3 * \text{Remote insulin}$$

'Minimal' model (sic)

Fig. 2. The minimal model. The first equation represents the physiological factors that determine the restoration of plasma glucose after injection: the effect of glucose itself (S_G), and the effect of insulin in the interstitial compartment [$X(t)$], which acts synergistically with glucose to return the glycaemia to basal levels. The second equation represents the flux of insulin from plasma into the interstitial compartment, where it acts [8]. dG/dt = Glucose restoration rate; G = plasma glucose; dX/dt = rate of increase in remote insulin; p_2 = fractional rate of insulin appearance in interstitial fluid; p_3 = fractional clearance of insulin from interstitial compartment; I(t) = plasma insulin; S_I = insulin sensitivity index; S_G = glucose effectiveness; X(t) = is proportional to remote insulin (i.e. insulin in interstitial compartment).

We reasoned that, although the closed-loop relationship between glucose and insulin remains intact during the test, the resulting data can be described by a stimulus-response (input-output) model of the extrapancreatic tissues that utilize glucose. The plasma insulin measured during the IVGTT represents the stimulus to the tissues utilizing glucose (fig. 1), and glycaemia is the response. What remained was to define a model that could accurately represent the effect of secreted insulin on glucose dynamics.

We applied the principle of Occam's Razor, i.e. by asking what was the simplest model based upon known physiology that could account for the insulin–glucose relationship revealed in the data. Such a model must be simple enough to account totally for the measured glucose (given the insulin input), yet it must be possible, using mathematical techniques, to estimate all the characteristic parameters of the model from a single data set (thus avoiding unverifiable assumptions). The emergent selected model, the minimal model, is represented in figure 2. We discovered that certain very fundamental physiological realities had to be represented in the model. (1) Glucose, once elevated by injection, returns to basal level due to two effects: the effect of glucose itself to normalize its own concentration (mass action plus allosteric effects of hexose [7]) as well as the catalytic effect of insulin to allow glucose to self-normalize (now known to be due to mobilization of glucose transporter 4). (2) Also, we discovered that the effect of insulin on net glucose disappearance must be sluggish – that is, that insulin acts slowly because insulin must first move from plasma to a remote compartment (later shown to be interstitial fluid) to exert its action on glucose disposal. The model embodies these simple ideas in two equations – one that relates glucose disappearance to the glucose effect (catalysed by insulin), and a second that describes the kinetics of insulin movement from blood to the active compartment (fig. 2).
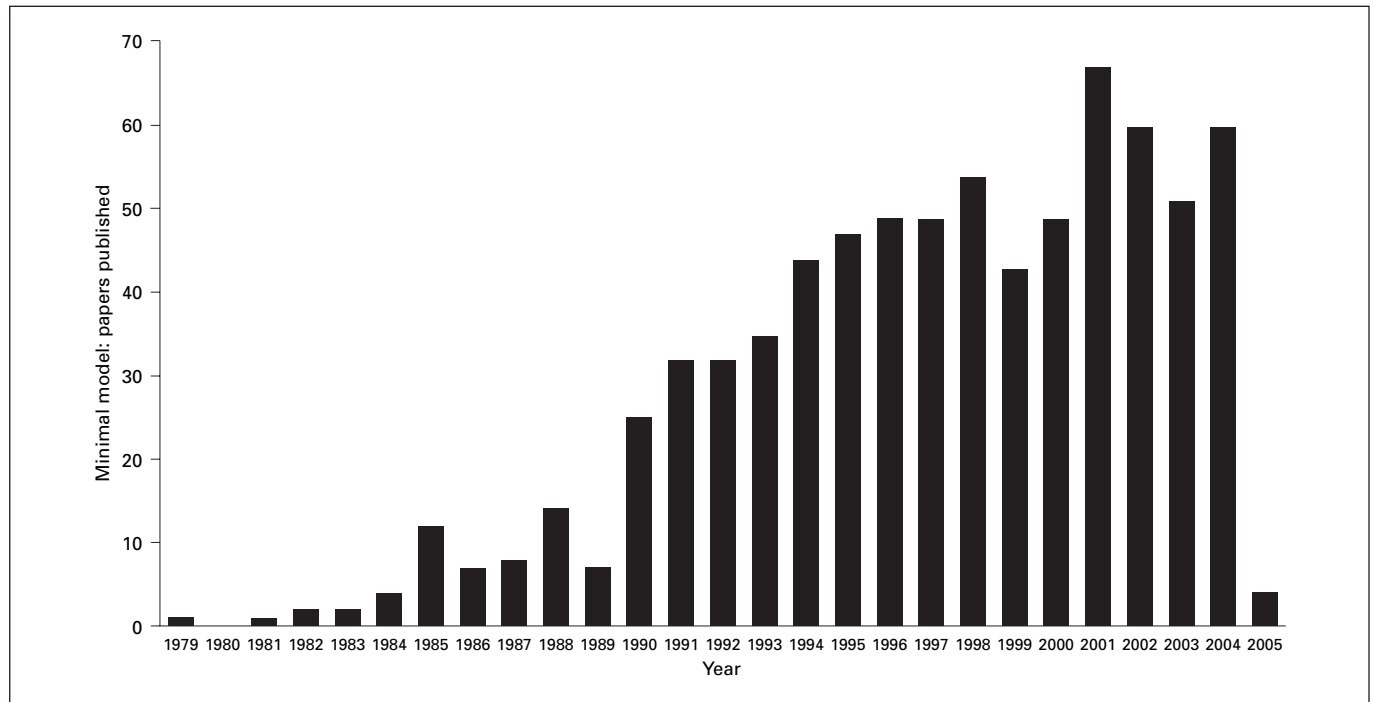
Fig. 3. Studies using or studying the minimal model from 1979 to April 2005, estimated from the PubMed Citation Index.

The Metabolic Profile

The mere presentation of a model of glucose homeostasis would have only didactic value if not applicable in real circumstances. We considered the descriptive parameters that could emerge from the modelling of the IVGTT, which might have usefulness for assigning risk for developing diabetes. It was clear even several decades ago that insulin resistance could be an important risk factor for type 2 diabetes. How could insulin resistance (or its converse, insulin sensitivity) be calculated from the minimal model? Insulin sensitivity was defined in quantitative terms as the effect of insulin to catalyse the disappearance of glucose from plasma.

In mathematical terms, this translated as the partial derivative of insulin (I) and glucose (G) upon net glucose disappearance:

$$\delta^2\,(dG/dt)/\delta G \delta I$$

in which G is the plasma glucose concentration and I is the plasma insulin concentration.

We showed that insulin sensitivity, which we defined as the insulin sensitivity index (S_I), could readily be calculated from parameters of the minimal model [8]. These

considerations made it possible to: (1) perform the frequently sampled IVGTT on an individual; (2) measure glucose and insulin; (3) fit the data to the minimal model; (4) calculate insulin sensitivity.

The value of S_I has been compared favourably many times with measures of insulin sensitivity from the glucose clamp [6]. To carry out this comparison it was necessary to discern the clamp analogue to S_I. In fact, S_I from the clamp represents the effect of insulin, per se, to augment the ability of glucose to enhance net glucose disappearance from the extracellular fluid (by suppression of endogenous glucose output plus increase in glucose disposal). The term S_I is often misused as a general term for insulin sensitivity whereas it should be used according to the formal definition given above (see Zethelius et al. [9] for an example).

In addition to S_I, we defined an additional parameter of glucose homeostasis: S_G, or glucose effectiveness – the ability of glucose itself to enhance its own disappearance independent of an increment in insulin. Additionally, we adopted the insulin secretory measure introduced by Porte and his colleagues: the first-phase insulin response ($AIR_{glucose}$). Thus, it is possible to obtain a comprehensive snapshot of glucose homeostasis from the ac-
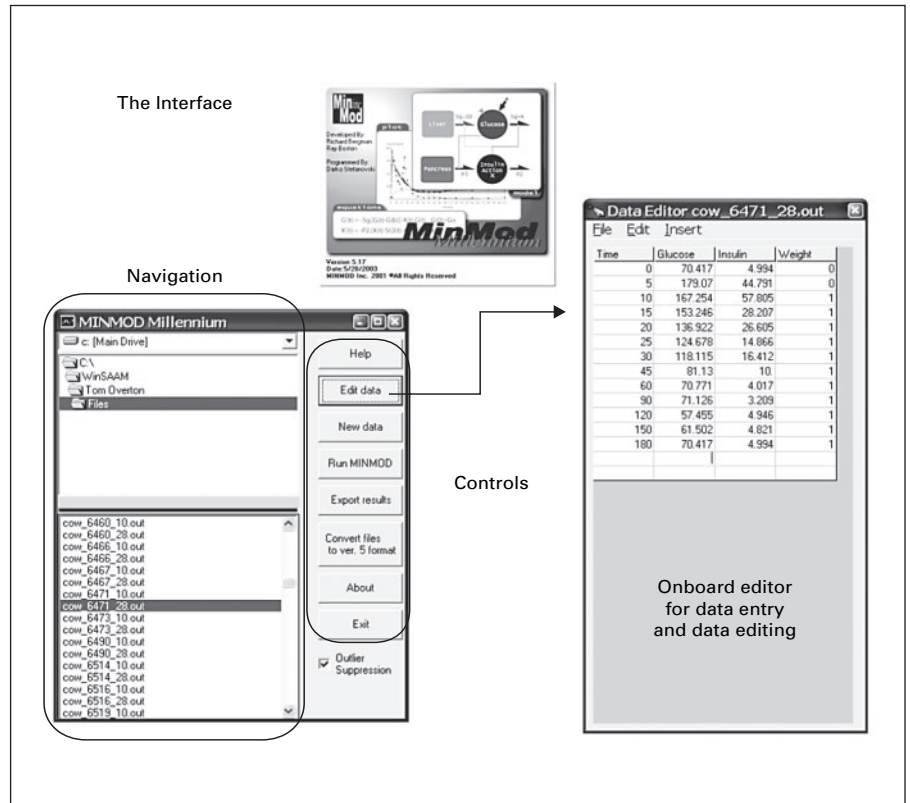
Fig. 4. Output from the user-friendly program Minmod Millennium (copyright R.N. Bergman).

cumulated parameters from the minimal model: S_I, S_G and $AIR_{glucose}$. The minimal model has been used in hundreds of studies, and the number of minimal model papers continues to increase (fig. 3), testifying to the longevity and usefulness of this modelling approach. One possible contributor to the longevity is the availability of 'friendly' software [10, 11], which allows independent investigators to calculate minimal model parameters without a sophisticated knowledge of the underlying mathematics (fig. 4).

Disposition Index and the Hyperbolic Law of Glucose Tolerance

The minimal model was first applied to human patients in 1981 [12]. In this study, we introduced the concept that there is a stereotypical relationship between insulin sensitivity and insulin secretion (fig. 5) [13]. Based upon the engineering principle of closed-loop gain, we hypothesized that in normal individuals, the product of insulin sensitivity and insulin secretion would be approximately constant; that is:

insulin sensitivity $\times$ insulin secretion = disposition index (DI)

$$S_I \times AIR_{glucose} = DI$$

This suggests that environmental reduction in insulin sensitivity (e.g. due to obesity, pregnancy, puberty, infection etc.) would be compensated for by an increase in β-cell function, thus avoiding an impairment in glucose tolerance.

The β-cell has the ability to upregulate insulin secretion in response to insulin resistance. The degree to which it is able to do this is represented by the DI, which is, therefore, a measure of β-cell functionality. That is, DI reflects the ability (or lack thereof) of the β-cells of the pancreatic islets to be able to compensate for insulin resistance by increasing β-cell responsivity. The latter process is possibly the most fundamental factor in the maintenance of normal glucose tolerance (and, in fact, normal fasting glucose) in the face of the vicissitudes of insulin sensitivity, which are inevitable in the modernized world. The DI can be conveniently represented as a hyperbola (fig. 5). Numerous studies have confirmed the ability of the β-cells to compensate for insulin resistance as pre-
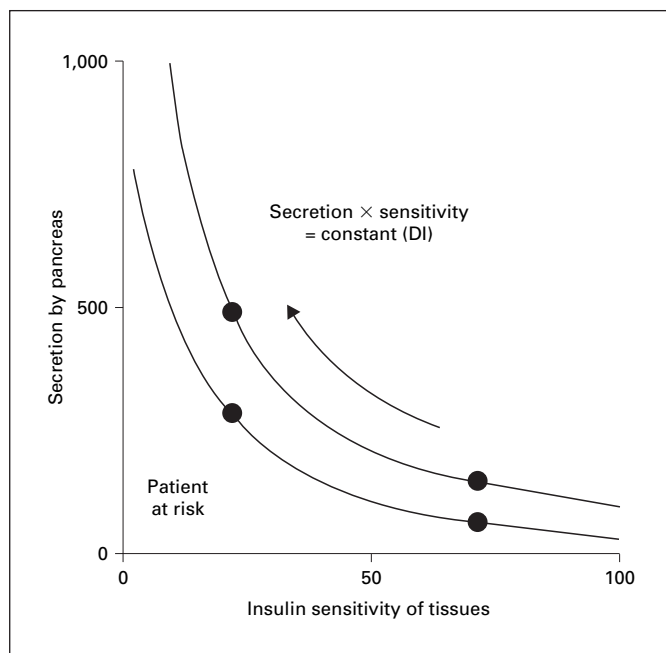
Fig. 5. Hyperbolic law of glucose tolerance. The hyperbolic curve represents the propensity of the pancreatic β-cells to upregulate insulin secretion in the face of insulin resistance. Thus, in normal states of insulin resistance such as pregnancy and puberty, insulin sensitivity is reduced and there is an appropriate increase in secretion to compensate for and maintain glucose tolerance in the normal range. Patients at risk for type 2 diabetes, however, operate on a curve nearer the origin, such that insulin resistance causes a lesser compensation in secretion. This can lead to glucose intolerance and, eventually, type 2 diabetes. The equation for each curve is *insulin sensitivity × insulin secretion = DI*. The latter is a measure of β-cell health (i.e. the ability of the pancreatic β-cells to compensate for insulin resistance). Figure adapted from Bergman [13].

dicted by the previous equation [14, 15], and the DI relationship has achieved the status of being referred to as a law: the hyperbolic law of glucose tolerance [16].

Prediction of Type 2 Diabetes

Traditionally, type 2 diabetes has been considered to be a disease that develops rather slowly and one for which obesity is a prominent risk factor, usually responsible for insulin resistance. With time, β-cell functionality slowly declines, until hyperglycaemia ensues. The precise event that causes the tipping point [17] from impaired glucose tolerance to fasting hyperglycaemia remains elusive. However, it is clear that both insulin resistance and decreased β-cell function are risk factors for diabetes.

It is now abundantly clear that intervention can delay, or possibly even prevent, type 2 diabetes. Various insulin-sensitizing protocols, including pharmacological [18] and lifestyle intervention [19], effectively prolong the period before the development of diabetes in individuals at high risk. Thus, it is very important to identify those at greatest risk for type 2 diabetes, so that resources for intervention can be judiciously applied. How may we identify those individuals most at risk?

Despite high expectations, a single gene responsible for type 2 diabetes has not been identified. Instead, several gene variants have emerged as possibly contributing to diabetes risk; among these nominated genes are the peroxisome proliferator-activated receptor γ gene as well as hepatocyte nuclear factor 4α and calpain-10. The search for genes contributing to diabetes risk continues.

In the absence of 'the' diabetes gene, other approaches to measuring diabetes risk must be used. One such putative measure is the DI. It is the reduction in the ability to compensate for insulin resistance that may predict disease. That this is true, at least in some populations, has been demonstrated by several groups. DI has been found to be a powerful predictor of type 2 diabetes in the Pima Indians of Arizona, with a difference in odds for diabetes (comparing lowest to highest decile of DI) of almost 20. In addition, Groop and colleagues [20] have recently shown that DI is the single most effective non-genetic predictor of diabetes in the Botnia study of diabetes genetics in Western Finland.

Genetics of DI

If DI can predict diabetes, and if gene loci have been identified that are linked to increased risk of diabetes, is there a gene for DI that may in fact be responsible for at least some cases of diabetes in a given population? Two groups have identified a locus on chromosome 11 that may be linked to diabetes. In the Insulin Resistance Atherosclerosis (IRAS) Family Study [21], quantitative linkage analysis was used in a genome scan, and the highest lod score identified (approximately 3) linked the DI to the locus on chromosome 11. The Finland–United States Investigation of NIDDM Genetics (FUSION) study of diabetes [22] confirmed this, and identified a locus for diabetes risk in a region that overlaps with the chromosome 11 risk from the IRAS study. Thus, the possibility exists that there is a gene on chromosome 11, which is heritable, that causes risk for type 2 diabetes, and which determines
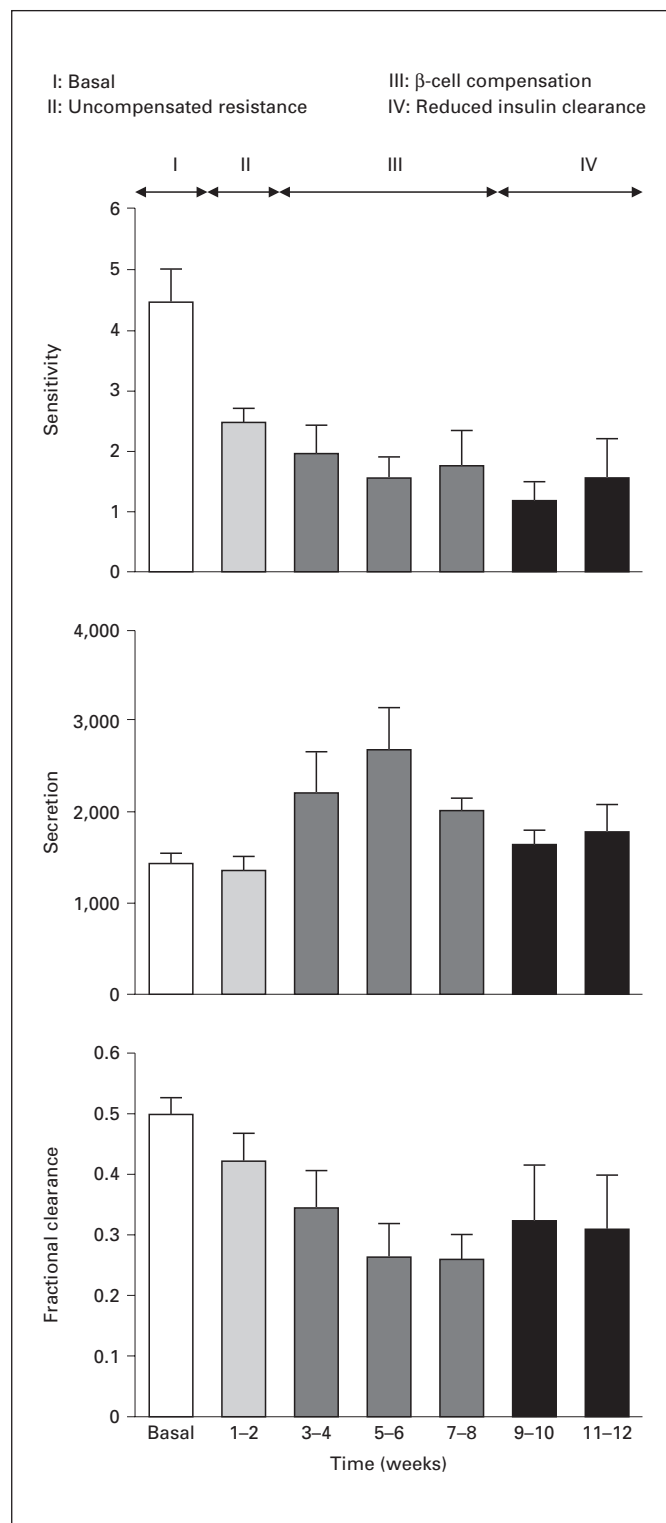
Fig. 6. Time course of compensation for insulin resistance in the dog model. Insulin resistance is induced by increased dietary fat, which is slowly compensated for by increased insulin secretion (maximal at 5–6 weeks) and a decrease in first-pass clearance of insulin by the liver [24].

the DI. Further studies will test the hypothesis that inheritance of the DI can explain at least some cases of type 2 diabetes.

Accounting for the Hyperbola

What physiological mechanism accounts for the robust hyperbolic relationship between insulin secretion and insulin sensitivity? Insulin resistance caused by a variety of mechanisms elicits the appropriate insulin response [23]. For example, induction of insulin resistance by fat feeding causes a rapid decline in insulin sensitivity (after 1 week), followed several weeks later by the appropriate degree of hyperinsulinaemia (fig. 6) [24], but how do the β-cells 'know' to increase secretion in response to insulin resistance? The classic concept is that insulin resistance results in a subtle glucose intolerance, which in turn causes mild hyperglycaemia leading to increased β-cell responsivity. However, in studies in the dog model, we reported substantial insulin resistance in the absence of any increase in plasma glucose. Nevertheless, plasma insulin still increased to compensate for resistance, and glucose intolerance was prevented. What is the mysterious signal that notifies the β-cells to increase insulin output?

The Mysterious Signal

Our laboratory carried out a systematic study to attempt to identify the signal for upregulation of insulinaemia. We considered the following possible endogenous secretory signalling mechanisms, which could conceivably act as signals:
1 fasting glucose
2 fasting free fatty acids (FFA)
3 nocturnal glucose and/or FFA
4 glucagon-like peptide (GLP)-1
5 cortisol
6 growth hormone
7 central nervous system.

As previously mentioned, we induced insulin resistance in the dog model by feeding a high-fat diet (6 g/kg/day). Dogs gained weight (~5 kg or 20% of body weight in 6 weeks), and demonstrated insulin resistance and hyperinsulinaemia. However, there was absolutely no increase in fasting glucose and no significant increase in fasting FFA. To examine possible nocturnal changes, we collected blood samples over 24 h under control (normal
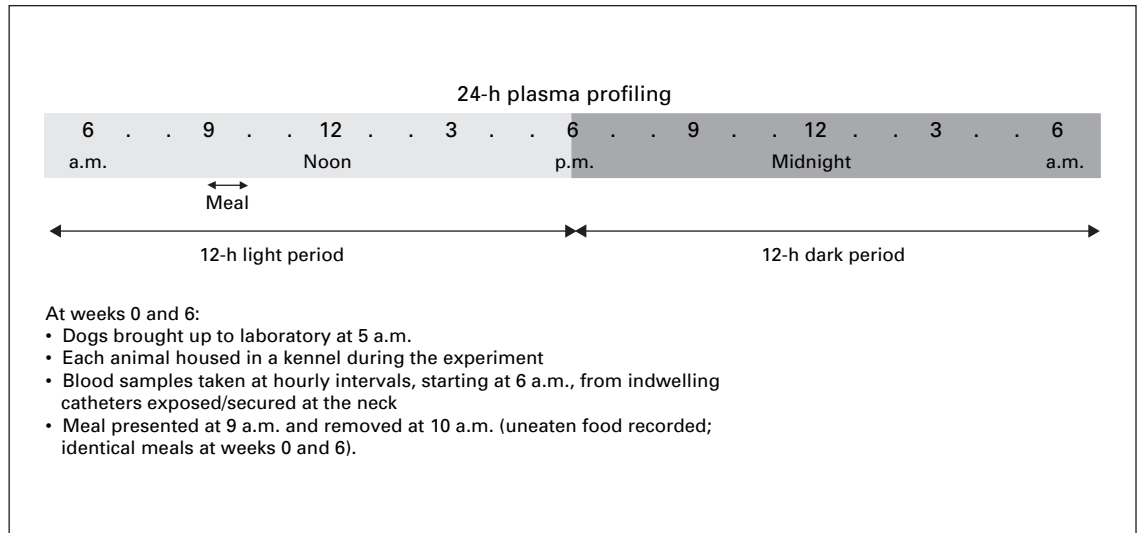
Fig. 7. Protocol for establishing changes in FFAs overnight in the dog model.

diet) conditions, and after 6 weeks on the high-fat diet (fig. 7). Again, there was no change in the glucose pattern, even over 24 h. Additionally, no increases were observed in 24-h patterns of GLP-1, cortisol or growth hormone. In sharp contrast, however, was a highly significant increase in FFA levels overnight: the 24-h pattern of FFA secretion was increased by 49%. On the basis of these results, we hypothesize that increased nocturnal FFA levels are the signal responsible for the insulinaemic compensation for fat-induced insulin resistance. Definitive proof will require pharmacological normalization of overnight FFA to see if the compensatory signal is suppressed.

Comment

The minimal model is now over 25 years old. It is somewhat surprising that it has lasted so long, but this may be regarded as a testament to the robustness of the model itself. Its longevity is also due to the fact that 'friendly' software (such as Minmod Millennium, copyright MINMOD Inc., Pasadena, California, USA) has been made available so that the model is accessible to individuals not necessarily conversant in differential equations. The model has been useful as a compass by which to identify important issues in systems biology as they relate to carbohydrate metabolism. While the model itself has not been changed, it is now being expanded to include fat metabolism (A.E. Sumner, personal communication).

It will thus be of interest to observe the next 25 years, to see whether this simple model with interesting characteristics further enhances studies of carbohydrate metabolism and diabetes. In particular, it will be of interest to see if the model's usefulness is reduced by genetics, or if it can continue to enhance studies looking for the cause of, and therapy for, type 2 diabetes and other insulin-resistant states.

Acknowledgement

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