Methods for assessing insulin sensitivity in man

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Introduction

Classically, insulin-dependent diabetes mellitus (IDDM) and non-insulin dependent diabetes (NIDDM) were considered to be disorders of insulin secretion. In IDDM, insulin secretion is totally lacking while it was assumed that there was a partial deficiency in NIDDM. More recently, it has been realised that in both conditions there is insulin resistance, and this may indeed be of major pathogenic significance, as well as of therapeutic importance in NIDDM. This has led to a search for simple, accurate and reproducible tests of insulin sensitivity in man in vivo.

The first tests were devised in the 1930s (Himsworth, 1936; Himsworth & Kerr, 1939) and comprised glucose tolerance tests with and without added insulin injection. Further developments awaited the introduction of the insulin immunosay. The modern era started with the pioneering work of Andres et al. (1966) and Reaven's group (Shen et al., 1970). Since then many tests have been devised. They can be divided into an 'indirect' or endogenous group where attempts are made to assess the effect of endogenous insulin and a 'direct' or exogenous group where insulin is infused and the effects on glucose metabolism are assessed. Each has its advantages and disadvantages and these are briefly discussed below.

Tests of endogenous insulin sensitivity

Basal state. Attempts have been made to use basal plasma glucose and insulin levels to assess insulin sensitivity in the resting state (Turner et al., 1979). It is obvious that if glucose levels are normal and insulin levels are raised, then there is insulin insensitivity. Problems arise when glucose levels as well as insulin levels are raised. In addition, much of the action of insulin in the resting state is on the liver, while insulin is measured in the periphery, portal levels being variably higher. No reliable index has yet been obtained although glucose/insulin or glucose/C-peptide ratios have been used as crude indices.

Oral glucose tolerance test (OGTT). This has been the time-honoured method for assessing insulin sensitivity. It has the advantage of relying on the subject's own insulin, but has several disadvantages. Both glucose and insulin levels are changing, making interpretation difficult. It is non-steady state; subtle changes in the rate of insulin secretion could have effects on insulin disposal, and variations in gastrointestinal absorption, and gut hormone secretion could confound the results. Bergman et al. (1979) have created a successful model of insulin sensitivity based on the OGTT, but it is difficult to validate.

Intravenous glucose tolerance tests (IVGTT). The IVGTT has advantages over the OGTT in that glucose absorption is no longer a significant variable and gut factors are not involved. Glucose disappearance is log-linear and can be expressed as percentage disappearance per minute ($K_g$). If the insulin response to the glucose is constant, then $K_g$ is an expression of insulin sensitivity. This is not the case, but the early insulin response is related to $K_g$ in normal man, and sensitivity can be expressed rather crudely as a ratio of these two.

More recently Bergman and his colleagues (see Bergman et al., 1985) have developed a model which allows a rather sophisticated expression of insulin sensitivity from a standard IVGTT with very frequent sampling (FSIGT). This is the 'minimal' model, so called because it is the simplest physiologically based model which can account for the input–output relationships under various conditions. It takes into account the rate of change of glucose and insulin, and memory for the insulin effect; insulin-dependent and insulin-independent glucose metabolism, and the effects of insulin on hepatic glucose production, peripheral glucose disposal. Several studies have now been reported comparing the minimal model FSIGT with the more conventional euglycaemic clamp method (see below). These showed a relatively poor correlation (Foley et al., 1985; Beard et al., 1986), particularly when insensitive subjects were included. The FSIGT was therefore modified by adding a tolbutamide injection after 20 min. This improved the correlations markedly (Bergman et al., 1987) and this modified minimal model is the FSIGT of choice. An alternative method with continuous infusion of glucose with model assessment (CIGMA) has been developed (Hosker et al., 1985), and also shown to correlate reasonably well with euglycaemic and hyperglycaemic clamps. Nonetheless, there are still doubts about the physiological meaning of the various glucose tolerance tests as measures of insulin sensitivity.

Tests of exogenous insulin sensitivity

Insulin tolerance test (ITT). The response of blood glucose to an intravenous bolus of insulin has long been used as rough guide to insulin sensitivity, but fell out of favour because of the obvious counter-regulatory hormone response as blood glucose fell. Recently, however, an excellent correlation has been found with the euglycaemic hyperinsulinaemic clamp in normal subjects (Bonora et al., 1987) using the decrease in glucose over the first 15 min of

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Abbreviations used: IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus; OGTT, oral glucose tolerance test; IVGTT, intravenous glucose tolerance tests; FSIGT, frequency sampling of insulin and glucose test; ITT, insulin tolerance test.
the ITT as an index. If substantiated this has obvious appeal because of its simplicity.

Euglycaemic hyperinsulinaemic clamp. This is now considered the 'gold standard' of tests of insulin sensitivity. Insulin is infused at a fixed rate for 2–3 h and a variable glucose infusion (guided by a simple computer model) given to maintain euglycaemia (DeFronzo et al., 1979). Sensitivity is expressed either as the terminal rate of glucose infusion (M) or M divided by the steady-state insulin level (M/I). Alternatively, if starting sugars are variable (as in diabetes) metabolic clearance rate can be calculated. This varies somewhat with glucose level, but probably not enough to alter interpretations of the test (Doberne et al., 1982). One key point is that sufficient insulin must be given to suppress hepatic glucose output completely. This should be checked isotopically, but this itself is not without problems. The assumption is also made that steady-state glucose infusion is reached in 2–3 h. This is certainly not the case.

Glucose insulin infusion tests. The first steady-state method involved the infusion of fixed rates of insulin and glucose together with propranolol and adrenaline to suppress endogenous insulin secretion (Shen et al., 1970). This was potentially unsafe and was replaced by insulin, glucose and somatostatin (Harano et al., 1977). We subsequently showed that if somatostatin was left out, there were still excellent correlations with the conventional clamp (Heine et al., 1985, 1986). This test is particularly simple, seems independent of starting glucose, and allows calculation of the metabolic clearance rate of glucose.

Conclusions

It can be seen that several methods have been described for assessing insulin sensitivity. Some are more suitable for widespread use. Ideally, however, dose–response curves should be constructed and for this either the clamp techniques or the glucose-insulin infusion are best. It is worth noting that 'insulin-sensitivity' in the context of these exogenous tests refers only to glucose disappearance, primarily into muscle. This is very limited and new tests are required to assess the many other actions of insulin, particularly in diabetes. This is now considered the 'gold standard' of tests of insulin sensitivity.

We are grateful to the British Diabetic Association, the Medical Research Council and Novo Industries for financial support.


Himsolworth, H. P. (1936) Lancet i, 127


Received 26 May 1987

Glucose homoeostasis in pregnancy and lactation

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Pregnancy and lactation are two physiological situations characterized by the development of new tissues the energy requirements of which have to be provided by the mother; namely, the conceptus and the mammary gland. These consume large amounts of glucose for fetal growth and metabolism (for reviews, see Battaglia & Meschia, 1978; Girard, 1985) and for milk lactose and lipid synthesis (for reviews, see Williamson, 1980, 1986; Williamson et al., 1984). The rat is an appropriate species in which to study the adaptations of glucose metabolism during these periods, since the fetal mass at term and the milk production at peak lactation represent a considerably higher nutritional demand than in other species, including the human (Table 1). Thus, the physiological adaptations of glucose metabolism in this species are expected to be exaggerated.

Glucose homoeostasis in the post-absorptive state

The extra glucose requirement for fetal growth and metabolism and for milk synthesis in the mammary gland are covered in part by a 20% increase in food intake during late pregnancy (for a review, see Girard et al., 1984), and by a 300% increase in food intake at peak lactation (for

Table 1. Comparison of fetal to maternal weight ratio and of milk production in several species

<table>
<thead>
<tr>
<th>Species</th>
<th>Fetal/maternal weight ratio (%)</th>
<th>Maternal milk production (g/day per kg body wt.)</th>
</tr>
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<tr>
<td>Man</td>
<td>6</td>
<td>20</td>
</tr>
<tr>
<td>Sheep</td>
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<td>50</td>
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<tr>
<td>Pig</td>
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<td>40</td>
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<td>Rabbit</td>
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<tr>
<td>Guinea-pig</td>
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<td>80</td>
</tr>
<tr>
<td>Rat</td>
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