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Alternative insulin delivery systems: how demanding should the patient be?

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When considering alternative insulin delivery systems, the patient should be very demanding and should insist on a system which results in metabolic control which is as close to normal as possible. In order to do this it will be necessary to simulate the normal profile of insulin secretion. In this article it is our purpose to review the normal patterns of insulin secretion in humans, to define the alterations which occur in states of glucose intolerance so that they can be avoided and to summarize the criteria which we believe will need to be incorporated in the ideal alternative insulin delivery system.

Normal patterns of insulin secretion on a mixed weight maintenance diet

Using an open two-compartment model of C-peptide kinetics and individually derived C-peptide kinetic parameters, we have derived insulin secretion rates by deconvolution of peripheral C-peptide concentrations [1–3]. The insulin secretory profile in normal subjects on a weight maintenance diet showed that basal insulin secretion rates were 50.9 ± 4.8 pmol $\cdot$ $m^{-2} \cdot min^{-1}$ and the total amount of insulin secreted over a 24-h period was 145.8 ± 8.8 nmol $\cdot$ $m^{-2} \cdot 24\text{-}\ h^{-1}$. Following meal ingestion the insulin secretory response was rapid and insulin secretion increased approximately fivefold over baseline to reach a peak within 60 min (Fig. 1). In these studies subjects consumed 20% of calories with breakfast and 40% with lunch and dinner, respectively. However, the amount of insulin secreted after each meal did not differ significantly. The rapidity of the insulin secretory response to breakfast is underscored by the fact that 71.6 ± 1.6% of the insulin secreted in the 4 h following the meal was produced in the first 2 h and the remainder during the following 2 h. Insulin secretion did not decrease as rapidly after lunch and dinner and 62.8 ± 1.6 and 59.6 ± 1.4% of the total meal response were secreted in the first 2 h after these meals.

The normal insulin secretory profile is characterized by a series of insulin secretory pulses. After breakfast 1.8 ± 0.2 secretory pulses were identified in normal volunteers and the peaks of these pulses occurred 42.8 ± 3.4 min after the meal. Multiple insulin secretory pulses were also identified after lunch and dinner. After these meals up to four pulses of insulin secretion were identified in both groups of subjects. Thus, in the 5-h time interval between lunch and dinner an average of 2.5 ± 0.3 secretory pulses were identified and 2.6 ± 0.2 in the same period after dinner.

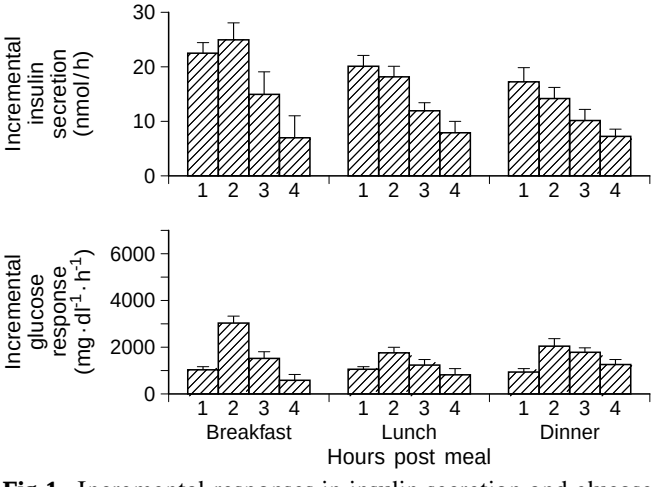

Fig. 1. Incremental responses in insulin secretion and glucose to ingestion of breakfast, lunch and dinner in normal volunteers. The responses in each of the first 4 h after meal ingestion are depicted. Adapted from Polonsky et al. [8]

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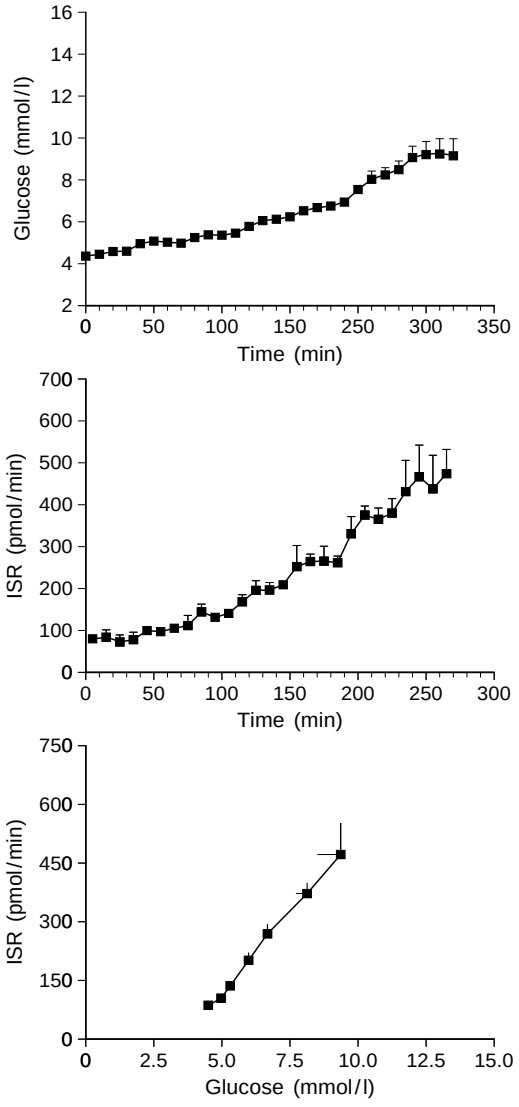

Fig. 2. Plasma glucose, insulin secretion rate (ISR) and the dose-response relationship between glucose and insulin secretion rate in a group of non-diabetic lean subjects. From Byrne et al. [5]

Pulses of insulin secretion that did not appear to be meal related were also identified. Between 23.00 and 06.00 hours and in the 3 h before breakfast on average 3.9 ± 0.3 secretory pulses were present in normal subjects. Thus, over the 24-h period of observation, a total of 11.1 ± 0.5 pulses were identified in normal subjects. Close to 90 % (87 ± 3 %) of post-meal pulses in insulin secretion, but only 47 ± 8 % of non-meal related pulses were concomitant with a pulse in glucose.

Insulin secretory responses to alterations in glucose, fasting and refeeding

Another important feature of the normal beta cell is its exquisite sensitivity to alterations in the plasma glucose concentration. We have studied this process using

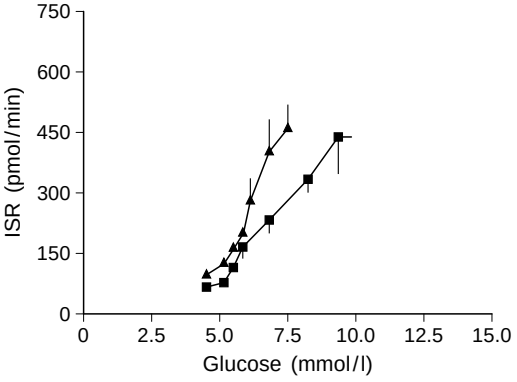

Fig. 3. After 42 h of glucose priming, the dose-response curve relating glucose and insulin secretion rate (ISR) is shifted significantly to the left. From Byrne et al. [5]

constant and oscillatory exogenous infusions of glucose [4]. If glucose is infused at a constant rate into normal volunteers all the subjects exhibit significant pulses of glucose, insulin and insulin secretion. On average during constant glucose infusion the mean period of insulin secretory oscillations was 126 ± 5 min. We subsequently administered slow and rapid oscillatory infusions of glucose in which the rate of the glucose oscillations was varied to be 20 % faster or slower than the endogenous rate of secretory oscillations. The insulin secretory response adjusted to the oscillations in glucose. The beta cell was able to detect and then respond appropriately to the successive increases and decreases in plasma glucose concentrations and this resulted in virtually complete concordance between glucose and insulin secretory pulses. This phenomenon is termed 'entrainment'. We have also studied the interactions between glucose and insulin secretion rate by measuring insulin secretion rates during graded glucose infusions [5]. Glucose was infused into normal volunteers at rates between 1 and 8 $mg \cdot kg^{-1} \cdot min^{-1}$. This raised the plasma glucose concentration over a physiologic range starting at 4.89 ± 0.07 mmol/l to reach peak levels of approximately 9 mmol/l (Fig. 2). Over this concentration range there is a very steep increase in insulin secretion in response to a modest increase in glucose (Fig. 3).

In order to determine if the dose-response relationships between glucose and insulin secretion could be modified by physiologic factors, glucose was infused continuously at a rate of 4 $mg \cdot kg^{-1} \cdot min^{-1}$ for 42 h achieving average glucose concentrations of 6.41 ± 0.616 mmol/l. As shown in Figure 3, this resulted in a significant shift in the glucose insulin secretion rate dose-response curve to the left representing an increase of 53 %. Similar adaptation of the sensitivity of the beta cell to glucose was seen after fasting and refeeding. Normal subjects were fasted for 72 h and then restudied after a period of 42 h of refeeding. Refeeding resulted in a 77 % increase in the insulin secretion rate compared with the fasting study.

These data therefore demonstrate that the sensitivity of the beta cell to a glucose stimulus can be substantially modified by factors such as exposure to high glucose which increases beta-cell responsiveness; fasting, which reduces beta-cell responsiveness and refeeding, which results in a rapid increase in the ability of the beta cell to respond to a glucose stimulus. Alternative insulin delivery systems will need to achieve the same ends as the beta cell in varying the level of responsiveness to glucose.

Adaptation to insulin resistance

Since the dose-response curve between the insulin concentration and its biological actions are shifted to the right as a result of resistance to the action of insulin, maintenance of normal glucose tolerance is dependent on the ability of the beta cell to increase insulin secretion to overcome the insulin-resistant state. Obesity is the commonest cause of insulin resistance. Our studies have demonstrated that in obese, insulin-resistant subjects, insulin secretion rates are approximately double those seen in lean control subjects. However, if glucose tolerance is normal, the pattern of insulin secretion remains normal. This issue has been studied by other workers including Bergman et al. [6] who have demonstrated that there is a hyperbolic relationship between the acute insulin response to glucose and the insulin sensitivity index S_i. Failure of this adaptation will inevitably result in glucose intolerance and hyperglycaemia.

Heterogeneity of immunoreactive insulin

Under normal circumstances, the composition of immunoreactive insulin is heterogeneous. Using high performance liquid chromatography it is possible to demonstrate that approximately 90% of the immunoreactive insulin is insulin itself and the remainder proinsulin-related compounds. The latter most commonly consist of intact proinsulin as well as a proinsulin breakdown intermediate, usually des 31, 32 proinsulin.

Abnormal insulin secretion in glucose intolerance and diabetes

A series of insulin secretory abnormalities has been described in subjects with glucose intolerance and diabetes. These should be avoided if an alternative insulin delivery system is to reverse the metabolic abnormalities present in subjects with diabetes. The alterations which have been described in diabetic patients include quantitative abnormalities with reduced capacity to secrete insulin, particularly in response to elevations in glucose level, but also alterations in the patterns of insulin secretion, both in abnormal rapid insulin pulses [7] and in abnormal ultradian insulin secretory oscillations [8]. The 24-h insulin secretion profile on a weight maintenance mixed diet demonstrates a number of significant abnormalities [8]. Basal secretion represents a significantly greater percentage of total insulin secretion in diabetic subjects than in control subjects (58 ± 3.5 vs 47.3 ± 2.1%). In addition the temporal pattern of postmeal insulin secretion is abnormal. In contrast to the rapid increase in insulin secretion seen in the first and second hours after breakfast in normal subjects, only 51.2 ± 1.6% of the 4-h insulin secretory response occurs during this time in persons with diabetes. Increases in insulin secretion above pre-meal levels are significantly lower in diabetic than in control subjects. In addition, the pulses of insulin secretion are reduced in amplitude and those following meals are substantially delayed in diabetes. Furthermore, the tight interaction between glucose and insulin secretion which is present in control subjects with normal glucose tolerance is not found in subjects with diabetes. Thus, failure to entrain these oscillations with exogenous glucose [9] has been reported. We believe that this observation results from a failure of the feedback mechanisms between glucose and insulin secretion in diabetic patients. Even in the early stages of glucose intolerance there is evidence that the rapid insulin pulses become abnormal [10], the acute insulin response to glucose is inappropriately low for the degree of insulin resistance, entrainment of the ultradian oscillations is abnormal, and the dose-response curve relating glucose and insulin secretion begins to shift to the right [11]. Alternative insulin delivery systems which attempt to reverse the metabolic abnormalities present in diabetes need to compensate for or even correct these alterations.

The significant increase in proinsulin and proinsulin-related peptides in subjects with diabetes is well-documented. The role of this abnormality in the pathophysiology of the increase in glucose is less clear, however.

Characteristics of the ideal alternative insulin delivery system

In our opinion, the ideal alternative insulin delivery system will need to incorporate the following characteristics:

a) Closed loop system with a very rapid response time. This is essential in view of the importance of a rapid response in insulin secretion to mixed meal ingestion and glucose in order to prevent postprandial hyperglycaemia and to avoid hypoglycaemia as the glucose level falls. The system needs to accommodate

the significant time lags between the increase in insulin secretion and the suppression of hepatic glucose production and stimulation of peripheral glucose utilization [12, 13]. These lags coupled with a steep glucose-insulin delivery dose-response curve will inevitably lead to an ultradian oscillatory profile of the insulin secretory response [14]. In fact, data from a study using an artificial pancreas with a steep dose-response curve in patients with insulin-dependent diabetes demonstrated postprandial oscillations in glucose and insulin delivery rate with a period of around 2 h [15]. However, the need for a steep response curve to small increases in glucose above the basal level is highlighted by the fact that blunted responses at the low end of the dose-response curve will lead to a resetting of the fasting plasma glucose concentration, such as occurs in subjects with glucokinase mutations [16]. An essential component of a successful closed-loop system with a rapid response time will be the availability of reliable glucose sensors, and although recent strides in this area have been made [17], it remains a key obstacle.

b) Adaptation to changes in insulin sensitivity and fasting and refeeding. As outlined above the sensitivity of the beta cell to glucose is a dynamic function which can be influenced by a variety of factors extrinsic to the beta cell. The most important of these is probably day-to-day variation in insulin sensitivity, but other important factors include exposure to glucose, fasting and refeeding.

c) Site of delivery. Normally insulin is delivered into the portal system. Clearly, in a closed-loop system, subcutaneous delivery would be undesirable because of the long lag-time between the injection of insulin and its appearance in the plasma. As a consequence of this lag, a reduction in blood glucose would not lead to a quick reduction in plasma insulin, even if the insulin delivery was shut off rapidly. From a physiological standpoint, it is debatable whether portally delivered insulin is more effective than peripherally delivered insulin. However, when insulin is administered into the peripheral circulation, the first pass effect of the liver is avoided and this effectively increases insulin concentrations by close to 50%. This effectively reduces the rate of insulin degradation but will result in chronic peripheral hyperinsulinaemia. Studies in subjects who have received a pancreas transplant with systemic drainage have thus demonstrated that although the absolute insulin secretion rates are normal compared to those observed in a normal control subject, the serum insulin levels are significantly elevated [18]. If such hyperinsulinaemia is present in an artificial closed-loop system using i. v. insulin administration, potential long-term adverse effects of peripheral hyperinsulinaemia will need to be considered. Intraperitoneal insulin administration leads to a rapid absorption of insulin into the portal circulation [19] and should be considered for closed-loop systems.

d) Mode of delivery: constant vs oscillatory. Under normal circumstances insulin secretion consists of small amplitude rapid pulses which recur every 5–15 min and larger amplitude oscillations which recur every 90–120 min. We believe that the ultradian oscillations are the inevitable consequence of a closed-loop negative feedback system in which there are time delays between the increase in insulin concentration and its ability to suppress hepatic glucose production and stimulate peripheral glucose utilization. Thus, we anticipate that ultradian insulin secretory oscillations will be present in an appropriately designed closed-loop system. We have recently demonstrated in normal weight, non-diabetic subjects that the exogenous delivery of insulin into the systemic circulation led to a greater reduction in the plasma glucose concentration when the mode of delivery was oscillatory with a period of 120 min as compared to constant delivery [20]. This suggests that a closed-loop system in which ultradian oscillations are generated might in fact be desirable. The biological significance of the ultradian insulin secretory oscillations is still uncertain, however, particularly in states of insulin resistance.

e) Composition of immunoreactive insulin. It is not known at present if replacement of proinsulin together with insulin to create a more normal profile of insulin immunoreactivity has important implications for insulin action and metabolic control.

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