Insulin Secretion in Diabetes Mellitus

A brief review of the normal physiology of insulin secretion is given. The dual role of glucose to directly stimulate insulin release and to potentiate insulin secretion to other islet regulators is emphasized. The B cell of the pancreatic islet is discussed as a metabolic integrator for nutrients, modulated by neural and hormonal input. A feedback model for the normal regulation of glucose concentrations is also described. This model is based on a closed loop between the islet, the liver and peripheral tissues for the production and utilization of glucose. Diabetes mellitus with overt hyperglycemia is characterized by impaired pancreatic B-cell function; however, in noninsulin-dependent diabetic subjects, many aspects of insulin secretion are maintained by a compensatory increase in plasma glucose concentration. The model shows why this increase in plasma glucose occurs and the importance of this hyperglycemia to the restoration of insulin responses to nonglucose secretagogues, second-phase insulin secretion to glucose and basal insulin. The model can account for the usual stability of plasma glucose in noninsulin-dependent diabetes mellitus and the very high glucose levels and lack of glucose stability in insulin-dependent diabetes mellitus. Sulfonylurea drugs increase insulin secretion, but this increase is dependent on the glucose level. Thus, the augmented B-cell function can be masked by a decrease in plasma glucose concentrations. During long-term therapy, the insulin level and responses are unchanged despite lower concentrations of glucose. Therefore, it is hypothesized that sulfonylureas still act by enhancement of B-cell function.

Impaired insulin secretion is common in diabetes mellitus and is responsible for many of the metabolic abnormalities associated with this disease. In this review we will summarize the physiology of insulin secretion in normal and diabetic human subjects and attempt to clarify its contribution to general carbohydrate homeostasis in diabetes.

Normal Physiology. Insulin secretion occurs from the B cell of the islets of Langerhans in the pancreas. The secretory responses of this cell are best understood by separately examining glucose stimulation and nonglucose stimulation.

Glucose stimulation of the B cell: In normal man, glucose stimulation of the B cell results directly in insulin secretion. A multiphasic islet response has been demonstrated in both in vivo and in vitro studies [1-3]. In human subjects, the first phase begins soon (1 to 2 minutes) after the intravenous injection of glucose and is generally over within 10 minutes, even when plasma glucose concentration is kept constant by the intravenous infusion of glucose (square wave). A second phase of insulin secretion occurs subsequently and continues as long as the hyperglycemia persists [4]. During a standard intravenous glucose tolerance test, the first phase is completed within the first 10 minutes. The second phase begins approximately 10 minutes after the intravenous bolus of glucose and generally ends between 60 and 120
Figure 1. Schematic representation of insulin responses during an intravenous glucose tolerance test. Note that there is a sharp increase in insulin release after the administration of glucose (first phase) and then a more sustained insulin release (second phase).

First-phase insulin secretion in normal human subjects is not dependent upon steady-state endogenous prestimulus glucose levels [6,7]. However, second-phase insulin release to an endogenous glucose stimulus is proportionate to the steady-state glucose concentration immediately preceding the glucose challenge [6]. The higher the prestimulus glucose concentration, the greater the second-phase insulin release; the lower the prestimulus glucose concentrations, the less the second-phase insulin release.

Nonglucose stimulation and inhibition of the B cell: Nonglucose stimuli include other nutrient substrates, hormones and neural regulators. Other nutrient substrates include proteins and their breakdown products (i.e., amino acids), and fats and their breakdown products (i.e., fatty acids and glycerol). These substances can either be absorbed from the gut or may be endogenously produced.

Most amino acids have been shown to stimulate insulin release. Arginine and leucine are the two most potent stimulators [8,9]. An example of a normal insulin response to an intravenous pulse of arginine is seen in the first panel in Figure 3. Neutral fat, cholesterol, triglyceride, ketones and fatty acids, although effective in some species, do not directly stimulate insulin secretion in man [1,5,10]. Glycerol is relatively quickly converted to glucose, and this in turn results in insulin secretion. Therefore, in human subjects, glucose and amino acids are the major circulating nutrient stimulators of insulin secretion. After adsorption, these substrates and the insulin which they generate pass through the portal system to the liver where further metabolic processes
occur. The hepatocyte has both insulin and nutrients presented together, and appropriate nutrient storage, synthesis or release can occur.

Hormones from other endocrine glands also play a role in insulin secretion. Hormones from the gut (i.e., secretin, gastrin, gastric inhibitory polypeptide and cholecystokinin) have all been shown to have insulin-stimulatory properties [11-13]. During meals, these gut hormones, the parasympathetic system and the nutrients absorbed, determine the appropriate insulin secretion for the meal.

Intraislet hormones may also be important islet modulators. Pancreatic glucagon secreted from the A cells of the pancreas has been demonstrated to have insulin-secretory properties [14]. Somatostatin, which is secreted from the D cells of the pancreas, has inhibitory effects on insulin secretion [15]. Thus, changes in the secretion of these hormones within the pancreatic islet may directly affect the insulin secretion from the B cell [16,17]. Both serotonin and prostaglandin E have also been found in the pancreas in which they inhibit insulin release [18,19]. It has been proposed that alpha sympathetic stimulation results in an increase in islet prostaglandin E, which in turn increases islet serotonin, the net result of which is decreased insulin secretion [19,20]. Other hormones (such as glucocorticoids and growth hormone) cause insulin resistance and, as a result, have indirect effects on insulin secretion by altering glucose utilization (vide infra). In addition, these hormones may change glucagon or somatostatin secretion and modulate B-cell function indirectly [16,21,22]. Thus, hormones can play a major physiologic role in insulin secretion.

The pancreatic islet is also under neural regulation. Parasympathetic stimulation causes an increase in insulin secretion [23]. Since the parasympathetic nervous system is activated during gastric stimulation, such as eating, the increase in insulin that occurs during a meal is, in part, secondary to activation of the parasympathetic nervous system. Although sympathetic stimulation can also cause an increase in insulin secretion by a beta-receptor mechanism [11], alpha-receptor activation inhibits insulin secretion [24]. In the pancreatic islet, alpha-adrenergic receptor activity predominates over beta-receptor action [25-27]. Thus, during sympathetic activation, insulin release is suppressed, and this is an important factor in the hyperglycemia seen during stress [28]. This adrenergic suppression of insulin secretion during stress can occur both through the sympathetic nerves to the B cell and local norepinephrine release, and through systemic epinephrine release from the adrenal gland. Both the A cells (glucagon-producing cells) and the D cells (somatostatin-producing cells) are also under the influence of the autonomic nervous system [29-31]. Therefore, neural regulation of the pancreatic B cells could also be indirect, via the neural regulation of A and D cells. Thus, the net neural influence on the B cell would also include the neural responsiveness of all islet cells.

Recently, it has been shown that some of the nerve terminals of the pancreatic islet are rich in vasoactive intestinal polypeptide [32]. Vasoactive intestinal polypeptide has been shown to stimulate insulin secretion in vitro [33]. Therefore, it is possible that nerve-terminal vasoactive intestinal polypeptide may also act as a neurotransmitter to modulate insulin secretion.

![Figure 3.](image)

Figure 3. Insulin responses to the nonglucose stimulant, arginine, in normal and diabetic subjects. Mean fasting plasma glucose concentrations: normal subjects = 85 ± 3 mg/dl; noninsulin-dependent diabetic subjects = 172 ± 9 mg/dl; insulin-dependent diabetic subjects = 350 ± 30 mg/dl. The basal insulin levels were similar for the noninsulin-dependent diabetic subjects and normal subjects, as were the insulin responses to arginine for these two groups. The insulin-dependent diabetic subjects had no detectable insulin response to arginine, and basal insulin levels were lower than those in the normal subjects.
Glucose as a potentiator of nonglucose stimuli: Glucose also has important modulatory effects on insulin-secretory responses to nonglucose secretagogues [34]. Figure 4 shows that when the prestimulus glucose level is raised, insulin secretion is augmented in response to isoproterenol (a beta sympathetic stimulant). Throughout the physiologic range of plasma glucose concentration in human subjects (80 to 200 mg/dl), there is a linear relationship between the prestimulus plasma glucose concentration and the magnitude of the insulin response to isoproterenol [34]. This effect, which we have termed glucose potentiation, has also been shown for other nonglucose secretagogues such as secretin, gastric inhibitory polypeptide, vasoactive intestinal polypeptide and arginine [8,12,33,35]. The potentiation by glucose of insulin responses to nonglucose stimulants is similar to the potentiation of second-phase insulin release to an intravenous glucose challenge by an increase in the steady-state prestimulus glucose concentration [6]. Glucose potentiation can also play an important role in the basal state by modulating B-cell sensitivity to endogenous neural and hormonal signals.

B cell as an integrator: On the basis of the preceding considerations, one is led to the concept that in man the B cell works as a metabolic integrator. It integrates food-related nutrient concentrations with neural and hormonal signals to regulate the secretion of insulin. The over-all islet response is appropriate to the nutrients available and the neuroendocrine set at the time.

Feedback model for carbohydrate metabolism: In a nonstressed normal subject, who is not taking pharmacologic agents, the basal glucose level will tend to remain the same day after day because of the intrinsic feedback loop shown in Figure 5. For example, any tendency for the glucose concentration to increase is counterbalanced by an increase in insulin secretion and a suppression of glucagon secretion, which regulate hepatic glucose production and tissue glucose uptake to keep the plasma glucose concentration constant. If a subject gains weight or becomes insulin resistant for any other reason, blood glucose levels will increase, resulting in increased insulin secretion to compensate for the insulin resistance. In this way, the insulin and glucose levels are modulated so as to minimize changes in these concentrations while relatively normal production and utilization of glucose are being maintained.

Insulin Secretion in Diabetes Mellitus. Noninsulin-dependent diabetes (maturity-onset diabetes mellitus,
Figure 5. A model for steady-state regulation of plasma glucose. Plasma glucose has direct effects on the pancreas to increase insulin and decrease glucagon secretion during hyperglycemia, and to increase glucagon and decrease insulin secretion during hypoglycemia. Glucagon stimulates glucose production, and insulin suppresses glucose production from the liver and increases glucose uptake in muscle and fat. Glucose uptake is not insulin-dependent in the brain. Any change in hormone secretion or hormone sensitivity will be modulated by this loop to minimize the change in glucose concentration and maintain peripheral glucose utilization.

**Type II** is a syndrome that can be divided into two physiologic types: metabolic compensated and metabolic decompensated.

Compensated noninsulin-dependent diabetes (fasting plasma glucose 115 to 200 mg/dl) is characterized by obesity and insulin resistance [36]. When compared to weight-matched euglycemic subjects, these patients usually have normal or nearly normal basal insulin levels. When hyperglycemia is present (fasting plasma glucose concentration greater than 115 mg/dl), first-phase insulin secretion in response to an intravenous glucose challenge is markedly impaired [37]. There may even be a paradox decrease in insulin release during the first 10 minutes of a glucose challenge [38]. However, subjects with fasting plasma glucose concentrations less than 200 mg/dl have nearly normal insulin responses to nonglucose stimuli and second-phase insulin secretion to glucose [39] (Figures 2 and 3). Maintenance of these basal insulin levels and responses is dependent on the potentiating effects of the increased plasma glucose concentrations (Figure 6). We hypothesize that there is an initial decrease in insulin secretion in these patients which results in impaired carbohydrate utilization. This, in turn, leads to higher plasma glucose concentrations. The increased plasma glucose compensates for the impairment of islet function by augmenting the insulin response to nonglucose signals and the second-phase response to glucose, resulting in an increase to nearly normal insulin responses and maintenance of basal insulin secretion. As a result, carbohydrate production and utilization are restored to normal, but at the expense of the hyperglycemia. During meals, the higher basal glucose level also allows relatively normal responses to nonglucose meal-related stimulants and minimizes the impaired insulin response to a meal. Because of this feedback loop, the fasting plasma glucose concentration is the same day after day in these patients, just as in normal persons [40]. There is simply a new higher balance point for the plasma glucose level. Because first-phase insulin secretion is not dependent on the glucose level, it is not restored by the higher glucose level and remains the characteristic abnormal islet cell finding in such patients.

In decompensated noninsulin-dependent diabetes the fasting plasma glucose concentration is greater than...
300 mg/dl. We hypothesize that the greater the islet defect, the higher the plasma glucose level necessary to maintain a compensated state. When the glucose level that is necessary to maintain normal insulin secretion and glucose utilization exceeds the renal threshold for glucose reabsorption, then such compensation generally cannot occur. The plasma glucose level will depend more on the renal clearance of glucose than on islet function. As a result, the feedback loop between the glucose concentration and the islet B-cell function will be broken, and islet compensation will generally not be possible.

Figure 7 shows that in almost all subjects with fasting plasma glucose concentrations less than 200 mg/dl, the insulin response to isoproterenol is normal. However, essentially no patients with a fasting plasma glucose concentration above 300 mg/dl have normal responses. Figure 8 demonstrates this finding for the second phase response to a 20 g intravenous glucose tolerance test. Most patients with fasting plasma glucose concentrations less than 200 mg/dl have a second-phase response within the normal range. However, among subjects with fasting plasma glucose concentrations greater than 300 mg/dl, only one patient is within the normal range. In both Figures 7 and 8, some subjects with fasting plasma glucose concentrations between 200 and 300 mg/dl appear compensated (normal responses), and others are not (low responses).
Insulin-dependent diabetes: Insulin-dependent diabetes [juvenile-onset diabetes mellitus, type I] is characterized by severe B-cell dysfunction and usually is found in thin subjects whose ages at onset are usually less than 45 years [36]. Although the cause of this type of diabetes is different from that of noninsulin-dependent diabetes, the feedback model for carbohydrate regulation is still valid for understanding the changes of insulin secretion and carbohydrate metabolism observed. These subjects have virtually no glucose-stimulated insulin secretion (Figure 2) and have greatly decreased or nonexistent responses to nonglucose stimuli (Figure 3). However, the lack of insulin secretion is not total in all of these diabetic patients. Some insulin-dependent diabetic patients have measureable basal insulin concentrations. In addition, some insulin secretion can be demonstrated in many insulin-treated diabetic patients, as assessed by the measurement of connecting peptide [C-peptide] [41]. C-peptide is measured because it is released with insulin from the B cell but is not metabolized by the liver. Thus, during a small release of insulin, changes in C-peptide can be measured more easily. However, this small release of C-peptide can only be demonstrated during marked islet stimulation and at high circulating glucose concentrations. Furthermore, this minimal secretion is generally not sufficient to maintain metabolic homeostasis. Therefore, in the absence of exogenous insulin therapy, there is marked unstable hyperglycemia, proteolysis, lipolysis and ketosis. However, during insulin treatment, residual endogenous insulin secretion, when present, appears to simplify diabetes control [42].

After initial treatment, these subjects often demonstrate a “honeymoon” phase of reduced insulin requirement. The length of this honeymoon phase is variable. During this time, insulin secretion is partially restored, sometimes to the point that the patient no longer requires insulin treatment. Because this restoration of B cell function is usually temporary, the patient will require insulin therapy at a later date. Methods to minimize islet damage at the onset of insulin-dependent
Figure 9. Importance of the prestimulus glucose concentration to the effect of tolbutamide on the insulin response to 12 μg of isoproterenol. The tolbutamide infusion (7 mg/m²/min) caused a significant decrease in glucose levels but no change in insulin response to isoproterenol. When the decrease in plasma glucose during tolbutamide was prevented by a concomitant glucose infusion, augmentation of the insulin response was observed. Thus, the decrease in glucose masked the insulinotrophic effects of the tolbutamide. Adopted from Pfeifer et al. [53].

diabetes and prolong the subsequent honeymoon phase are currently being evaluated [43].

Sulfonylurea Drugs and Insulin Secretion. Sulfonylureas have direct effects to stimulate insulin release from the pancreatic B cell [44]. During oral treatment, basal insulin levels and secretory responses to various stimuli are initially (days) enhanced, but with more prolonged therapy (months) these responses return to pretreatment values [45-51]. Hence the insulinotrophic effects of long-term sulfonylurea therapy have been believed to be transient, and the persistent decrease in glucose concentration during therapy has been ascribed to nonpancreatic effects of the drug [52].

Consideration of the feedback regulation of glucose and insulin raises an alternate possibility. If the plasma glucose level is important to maintenance of insulin

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secretion, then the decrease of plasma glucose concentration that occurs during therapy may mask the insulinotrophic effects of these drugs. As shown in Figure 9, the decrease in plasma glucose concentration accompanying the administration of tolbutamide to normal subjects can mask the stimulatory effect of the drug. This study demonstrates that the insulin responses of normal subjects to the nonglucose stimulus, isoproterenol, are not different before and after an infusion of tolbutamide. However, when the glucose level is prevented from falling by a concomitant infusion of glucose, then there is a clear-cut augmentation of isoproterenol-stimulated insulin release during the tolbutamide infusion [53]. We have also demonstrated similar findings for the nonglucose secretagogue arginine and for the second-phase insulin response to intravenously administered glucose.

We hypothesize that during long-term sulfonylurea therapy, a similar phenomenon occurs. Initially, there is an increase in insulin release; this occurs before there is a decrease in plasma glucose levels. After longer therapy, there is a decrease in fasting plasma glucose concentration, but the insulin levels are now not significantly different from the values before treatment [45]. We suggest that this same insulin response actually represents an augmentation of insulin release by the sulfonylurea. In a sense, the sulfonylurea has substituted for glucose, allowing the same insulin secretion at a lower glucose level. Long-term studies to validate this concept are now in progress.

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