Essential biochemical design features of the fuel-sensing system in pancreatic β-cells

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The β-cells of the pancreas control the blood levels of glucose and other nutrients by secreting insulin. They sense blood nutrient levels not by using a classical receptor-signaling system, but by detecting the products of nutrient metabolism. Mutations in this pathway can cause diabetes or hypoglycemia.

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Introduction

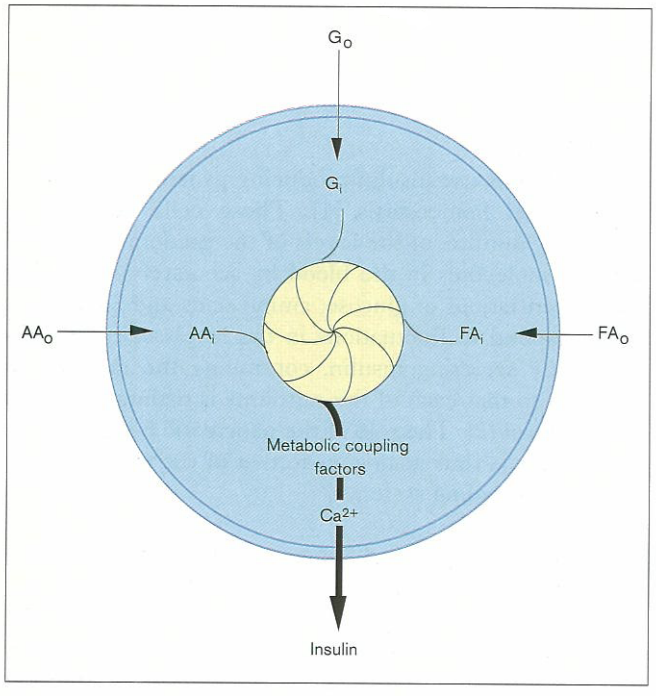
All vertebrates use insulin-producing pancreatic β-cells to provide fuel homeostasis [1]. These cells keep track, minute by minute, of the levels of the predominant small nutrient molecules in the blood by accurately measuring the concentrations of glucose, amino acids and fatty acids. They respond to fluctuations in the levels of these substances by secreting insulin, controlling the rate of the secretion so that each of the nutrients is maintained at its optimal level [2]. The role of the pancreatic β-cells in fuel homeostasis is thus analogous to that of the thermostat in heating and cooling systems.

The feedback loop of fuel homeostasis is completed by the insulin receptors in liver, muscle and adipose tissue that control fuel removal from the blood and, of course, by the regulated parameters of glucose, amino acids and fatty acids. In humans in the resting condition, these nutrient levels are ~5 mM for glucose, ~3.5 mM for the physiological mixture of 20 amino acids and ~0.3 mM for fatty acids. These levels refer to the postabsorptive situation, 8–12 h after a mixed meal containing carbohydrates, fats and proteins. Not surprisingly, blood fuel levels might be very different shortly after ingestion of a meal (postprandially) or after fasts of longer duration than 12 h [3]. Postprandially, most levels of blood fuel molecules can be expected to be higher than the values listed above; after starvation, the levels of certain amino acids and fatty acids are also elevated, due to mobilization of these fuels from muscle and adipose tissue, but blood glucose levels drop to about 4 mM. The pancreatic β-cells must distinguish between these different nutritional situations and release insulin in response to the meal but not the fast. In this brief review we discuss the biochemical mechanisms that enable the pancreatic β-cell to respond optimally to physiological fluctuations in the levels of nutrients in the blood, and describe some of the defects in these processes that can result in diabetes mellitus (the most common metabolic and endocrine disease afflicting several hundred million people worldwide) or less prevalent conditions of hypoglycemia.

The biochemical basis of fuel sensing

The biochemical engineering of the pancreatic β-cells uniquely equips them to operate as the body's fuelstat [2]. One might have imagined that these fuelstat cells might contain specific nutrient receptors that would recognize and measure the levels of small nutrient molecules including glucose, palmitic acid and the different physiologically important amino acids, and that this sensing system might be coupled to insulin secretion by one or more of the well

Figure 1



The metabolic wheel of insulin release from β-cells. Insulin release is stimulated by small nutrient molecules. G, glucose; AA, amino acids; FA, fatty acids; the subscripts o and i refer to outside and inside the cell, respectively.

known intracellular signaling pathways involving second messengers such as cAMP and Ca^{2+}. Such mechanisms are known to operate for the other chemical senses of smell and taste [4]. But the fuel-sensing system of β-cells uses a quite different principle. Nutrient sensing relies entirely on nutrient metabolism: special intracellular metabolic coupling factors detect the intermediary metabolism of nutrient stimuli and link it to the second messenger systems that are universally employed in biological systems (Fig. 1). Here, we describe the signaling pathways for glucose, amino acids and fatty acids as stimulants of insulin release.

Glucokinase, the β-cell glucose sensor

Blood glucose is the most effective stimulus of insulin secretion [2]. When levels of blood glucose increase, hormone secretion is enhanced with a characteristic dependency on the blood sugar level. The threshold for stimulation is ~5 mM. Secretion reaches half maximal efficiency at ~10 mM and is maximal at 20–30 mM. Physiological blood sugar levels rarely rise above 7.5 mM, however. Pancreatic β-cells have very effective facilitated membrane transport systems for glucose, so intracellular and extracellular glucose levels rapidly equilibrate [2]. Thus, the intracellular glucose level, which determines the rate of glucose metabolism that is required to stimulate insulin release, is a reliable indicator of the extracellular glucose level. The glucose-phosphorylating enzyme glucokinase (also termed hexokinase D), which phosphorylates glucose on C6, is central to the process of glucose metabolism in pancreatic β-cells. The kinetic characteristics of the enzyme explain how the concentration of glucose controls the rate of glucose phosphorylation, glycolysis and — to a considerable extent — glucose oxidation.

Biochemistry of glucokinase

Glucokinase is a 50 kDa monomeric hexokinase that phosphorylates the D-forms of glucose, mannose, glucosamine and fructose with different kinetics for each sugar. Because D-glucose is the preferred physiological substrate of the enzyme and because of the enzyme's characteristic low affinity for glucose, it is conventionally called glucokinase to differentiate it from other hexokinases which have much higher affinities for these six carbon sugars. The level for the half saturation of glucokinase with D-glucose ($S_{0.5}$) is 6–12 mM [2]. The rate constant k_{cat} at 37°C for glucose is about $100\,s^{-1}$ and the high Hill number for glucose, 1.8, indicates that the enzyme functions cooperatively. Remarkably, the enzyme does not show feedback inhibition by its product, glucose-6-phosphate. In liver, glucokinase activity is modified by a protein (the glucokinase regulatory protein, GRP) but this is probably not significant in pancreatic β-cells. Stearyl-CoA and palmityl-CoA also inhibit the enzyme competitively with glucose, with very low K_i values (1–2 μM). These are the only glucokinase inhibitors known to be important in β-cells.

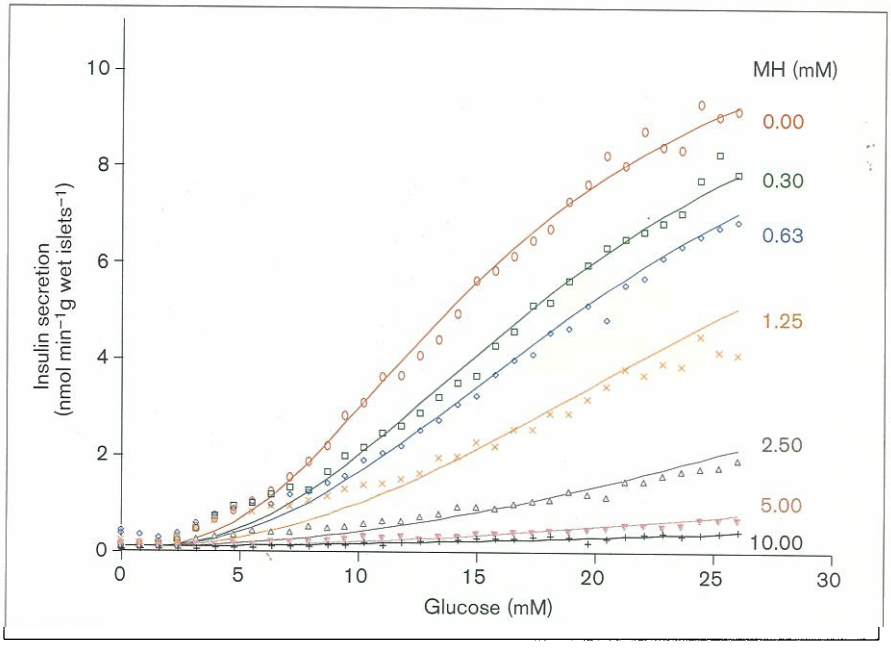
Glucokinase has been found in β-cells, in liver cells and in some neurons of the central nervous system. In β-cells, the enzyme is inducible by glucose by translational or post-translational control mechanisms. There is considerable support for the idea that high glucose stabilizes the enzyme and thereby decreases its turnover and raises its tissue level. In contrast, in the liver, glucokinase is induced by insulin through increased transcription. In pancreatic β-cells, the enzyme governs the rate of glycolysis so strongly that glycolysis changes in direct proportion with changes in the enzyme content of the cells. Glucokinase thus absolutely controls glycolysis in these cells. Because the rate of glucose metabolism in turn controls insulin secretion, it has been suggested that glucokinase is the glucose sensor of the β-cell.

Effects of glucokinase deficiency

The hypothesis that glucokinase functions as a glucose sensor has been strongly supported by clinical findings in humans [5] and by extensive work with transgenic animals [6]. Patients with a dominantly inherited familial form of diabetes mellitus (MODY II) were found to have mutations in one of the glucokinase alleles. Those mutations have been shown to increase the $S_{0.5}$ for glucose, lower the k_{cat} or decrease the stability of the enzyme [2,7]. From these and other observations, one can conclude that the functional β-cell glucokinase of these MODY II patients

Figure 2

The control of glucose-induced insulin release by glucokinase. Graded inhibition by mannoheptulose (MH) causes a graded block of insulin release from pancreatic islets. The K_i of MH for glucokinase is about 1 mM. Symbols indicate experimental data and continuous curves represent the results of model calculations [7].



may be reduced to ~50% of normal, which is sufficient to explain their impaired insulin secretion and mildly diabetic phenotype. Mice with a specific knockout of β-cell glucokinase become severely diabetic and die quickly after birth whereas transgenic mice that retain one normal glucokinase allele are mildly diabetic, resembling patients with MODY II [6]. All proven MODY II patients are heterozygotic, with one wild-type and one mutant glucokinase allele, implying that homozygocity is lethal in humans. The control of glucose-stimulated insulin release by glucokinase is most impressively demonstrated by a model experiment with isolated perifused islets from the pancreas [8]. Using mannoheptulose — a specific inhibitor of glucokinase — it can be demonstrated that reduction of phosphorylation by less than 20% causes a predictable reduction in glucose-stimulated insulin release (Fig. 2), similar to that seen in MODY II patients. This shows the importance of glucokinase in controlling the response of the β-cell to glucose.

The biochemical basis of metabolic coupling

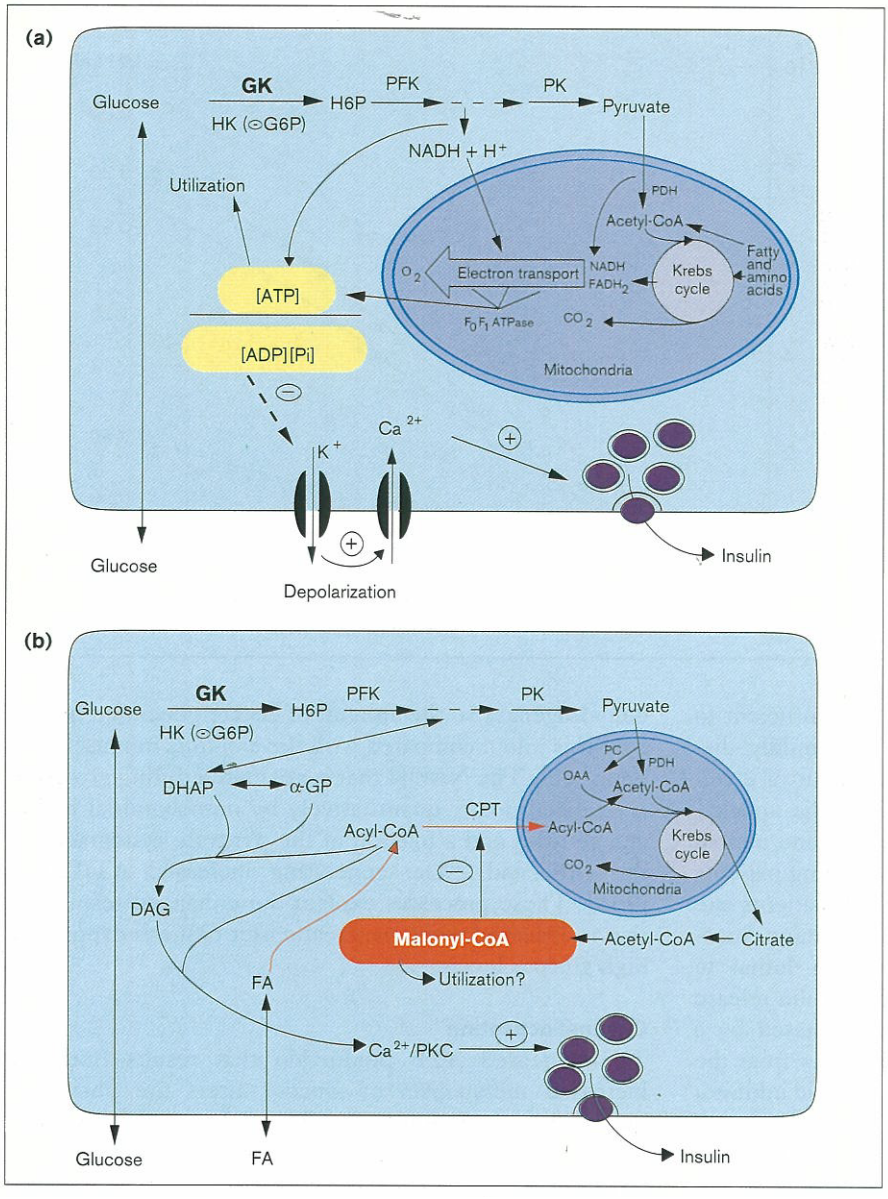
How is the increase in glucose metabolism coupled to insulin release? Increased glucose phosphorylation enhances glycolysis, glucose oxidation and respiration and, by extrapolation, should increase the rate of ATP generation in stimulated β-cells (Fig. 3a). The channeling of glucose through the catabolic pathways is facilitated by the fact that there are practically no synthetic pathways in β-cells that might syphon off glucose metabolites. For example, glycogen and fatty acid synthesis, which are important pathways in liver cells, are virtually absent in β-cells. Furthermore, β-cells have low levels of lactate dehydrogenase so the amount of lactate generated by glycolysis is minor compared with the amounts in muscle and brain cells. The NADH that is generated during glycolysis is oxidized nearly quantitatively by mitochondrial hydrogen shuttles and a fraction of the pyruvate is degraded in the citric-acid cycle, generating increased ATP levels [9,10]. These processes explain the enhanced respiration that is observed when pancreatic islet tissue is exposed to high glucose levels.

Channel activation

The increased ATP production that results from the increased metabolism of glucose alters the phosphate potential by increasing the ATP:ADP ratio of the β-cell cytosol. This change is recognized by adenine-nucleotide-sensitive K^+ channels of the β-cell membrane. ATP^{4-} inhibits and $MgADP^-$ activates the channel; thus an increase in the ATP:ADP ratio leads to inhibition of the channel and depolarization of the β-cell membrane. This depolarization opens voltage-sensitive calcium channels and elevates intracellular Ca^{2+}, the most important second messenger. The increased levels of free cytosolic Ca^{2+} in turn cause insulin release from stored insulin-containing granules, and this is enhanced by the activation of protein kinases A and C (see below). The biochemical basis of the exocytosis of insulin granules is currently the target of intensive research efforts [11].

The crucial role of adenine-nucleotide-regulated potassium channels has been underscored by studies of the molecular genetics of a particular form of familial hypoglycemia [12,13]. Infant patients afflicted by this disorder were found

Figure 3



Metabolic coupling in nutrient stimulation of pancreatic β-cells. **(a)** The pathway for the generation of ATP and **(b)** the pathway for generating lipid-related coupling factors. The following abbreviations are used: α-GP, α-glycero-P; CPT, carnitine palmityl-CoA transferase; DAG, diacylglycerol; DHAP, dihydroxyacetone-phosphate; FA, fatty acids; GK, glucokinase; HK, hexokinase; H6P, hexose-6-phosphate; OAA, oxalacetic acid; PC, pyruvate carboxylase; PDH, pyruvate dehydrogenase; PFK, 6-phosphofructokinase; PK, pyruvate kinase; PKC, protein kinase C. Other abbreviations are self explanatory. (From [2].)

to have mutations of a protein modifier of the potassium channel called the sulfonyl urea receptor (SUR) which results in persistent inhibition of the channel, concomitant membrane depolarization and insulin hypersecretion.

Lipid signaling molecules

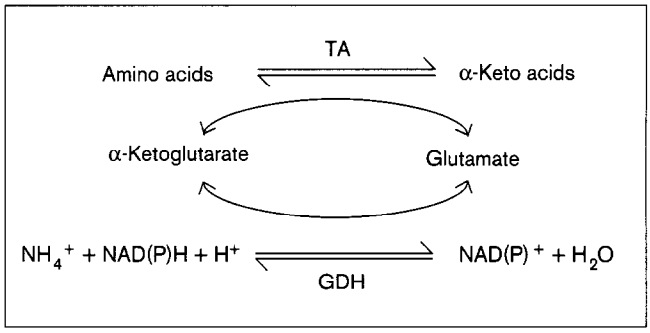
The pathway of glucose metabolism outlined above also leads to the generation of other metabolic coupling factors in addition to ATP (Fig. 3b). Most important among these proposed coupling factors are lipid-related molecules such as malonyl-CoA, palmityl-CoA and stearyl-CoA [2]. Malonyl-CoA is derived from citrate via the citrate lyase and acetyl-CoA carboxylase reactions. It inhibits carnitine palmityl transferase, a critical step of fatty-acid oxidation, and therefore causes acyl-CoA to accumulate in the cytosol. Acyl-CoA activates protein kinase C in a Ca^{2+}-dependent manner both directly and indirectly (after conversion to diacylglycerol), and therefore enhances insulin secretion.

Amino acids and fatty acids as fuel stimuli

The amino acids and fatty acids that are derived from a mixed meal have been shown to stimulate insulin release in humans [14]. Amino acids and fatty acids are glucose-dependent secretory stimuli; unlike glucose, they cannot by themselves cause insulin secretion [2]. These nutrients can only act as insulin secretagogues when the level of glucose is higher than 5 mM. This makes sense, because it allows them to be mobilized from muscle and adipose

tissue during starvation, when blood glucose levels are low. In this circumstance, insulin secretion ceases and glucose levels are then maintained by hepatic gluconeogenesis, which produces glucose from specific amino acids and lipid-derived glycerol.

Figure 4



The transdeamination of amino acids. TA, transaminases; GDH, glutamate dehydrogenase. Transamination reactions occur in the cytosol and oxidative glutamate deamination takes place in the mitochondrial matrix. The α-ketoacid products of the transamination reaction are catabolized further by the diverse pathways of amino acid metabolism. Glutamate and α-ketoglutarate (in addition to other transport metabolites) are shuttled back and forth across the mitochondrial membrane.

Amino acid transport and deamination

How do amino acids and fatty acids cause insulin release? Amino acids can be assumed to be transported into the β-cells by several transporters that are well characterized in other tissues and probably present in β-cells. Most of them are then likely to be transaminated by a family of pyridoxal-P-dependent enzymes that transfer the amino group to α-ketoglutarate to form glutamate [15]. The carbon skeletons of the amino acids are converted to pyruvate, acetyl-CoA, α-ketoglutarate, succinyl-CoA, fumarate and oxalacetate, and provide substrates for the citric-acid cycle. Glutamate serves as the predominant final product of the transamination reactions and is oxidatively deaminated, a process termed transdeamination (Fig. 4). For the system to operate it is necessary that at least one product of the citric-acid cycle (preferably the final product) be removed continuously. One way this is accomplished is to convert malate to pyruvate via the oxidative malic enzyme reaction (i.e. malate + $NADP^+$ ⇔ pyruvate + $NADPH^+ + H^+ + CO_2$). This allows most of the amino acids to be metabolized to CO_2, H_2O and NH_4^+. Amino acid degradation is hypothesized to generate the same coupling factors that are derived from glucose metabolism, ATP and malonyl-CoA.

In the normal pancreatic β-cell the critical reaction of transdeamination, catalyzed by glutamate dehydrogenase (GDH), appears to be far from equilibrium so that oxidation of glutamate is largely inhibited. Thus, little ATP and malonyl-CoA would be generated from amino acids, explaining the lack of response when amino acids are present in the absence of glucose. High levels of GTP and low levels of free ADP may be responsible for this inhibition but other factors, so far unknown, may also be important. The stimulation of insulin release by amino acids in the presence of glucose may be due to enhanced production of pyruvate, α-ketoglutarate and oxalacetate that would result from even a small increase in glucose metabolism. These metabolites can act as acceptors for the transamination reaction, and should therefore enhance the degradation of amino acids, allowing them to potentiate the stimulatory effect of glucose. Evidence for this view comes from experiments using artificial stimulators of glutamate dehydrogenase [16], which, under certain conditions, cause insulin release in the absence of glucose.

The importance of the GDH-catalyzed reaction in the amino-acid-stimulated release of insulin is supported by the biochemical and genetic elucidation of a hypoglycemia syndrome associated with hyperinsulinemia and mild hyperammonemia (C. Stanley, Children's Hospital of Philadelphia, personal communication). Infant patients afflicted by this disease have mutations of GDH, such that the inhibition of the enzyme by GTP or its activation by ADP are reduced or enhanced, respectively. Stanley proposes that in these patients the GDH reaction tends toward equilibrium, resulting in increased glutamate oxidation and generation of metabolic coupling factors even when glucose levels are low.

A large body of experimental and clinical evidence suggests that regulation of GDH in pancreatic β-cells is critically important for amino-acid-stimulated insulin release and that the enzyme is probably activated only when the blood sugar falls below critical levels [17]. Leucine is particularly effective in this regard. This would explain the leucine hypersensitivity that has been observed in hypoglycemia patients. Removal of the negative control of the enzyme by genetic mutation, in transformed β-cells or by pharmacological intervention may cause insulin hypersecretion and hypoglycemia.

Fatty acids as insulin secretagogues

Fatty acids can also trigger the glucose-dependent secretion of insulin [2,18]. Again, it makes sense that this response should be glucose dependent, as this ensures that the physiological surge of free fatty acids that occurs during starvation is not perceived as a stimulus for insulin release. Under some circumstances, high levels of fatty acids may also inhibit the glucokinase glucose sensor because acyl-CoA, the first metabolite in fatty acid catabolism, is a very potent inhibitor of this enzyme [2]. But this inhibition is competitive with glucose, and is therefore

significant only when glucose levels are < 5 mM. If glucose levels are high (~7.5 mM), as seen after a mixed meal, fatty acids can stimulate insulin release.

Several different metabolic coupling factors have been considered to be involved in the insulin response to fatty acids [2]. First, ATP production is probably increased. Second, as acyl-CoA and diacylglycerol are generated from fatty acids in the presence of high glucose, protein kinase C may be activated (Fig. 3b). Some investigators have suggested that the activation of protein kinase C is essential for glucose-stimulated insulin release, not just a contributory factor [19]. When the generation of acyl-CoA and diacylglycerol is blocked by hydroxycitrate (an inhibitor of the cytosolic enzyme citrate lyase that cleaves citrate to acetyl-CoA and oxalacetate; see Fig. 3b), insulin release is also blocked, supporting this view. Palmitic acid was found to overcome the effect of this enzyme inhibitor on glucose-stimulated insulin release.

General hypothesis of fuel-induced insulin release

The simplest general hypothesis of fuel-stimulated insulin release envisions that ATP serves as the essential general metabolic coupling factor that is generated by the activation of intermediary metabolism. Malonyl-CoA acts as a secondary stimulus by producing acyl-CoA and diacylglycerol, which may potentiate the effect of ATP depending on the nature of the stimulus. Glucose is required for amino-acid stimulation of insulin release because it is needed to provide α-keto acids as substrates for transaminations. In the case of fatty acids, glucose is needed to redirect lipid metabolism from degradation to the synthesis of lipid-related coupling factors.

There is increasing evidence that this may not be the whole story, however. It has recently been suggested that cyclic ADP-ribose and diadenosine polyphosphate (DAPP) can both function as metabolic coupling factors [20,21]. Cyclic ADP-ribose is thought to mobilize Ca^{2+} from intracellular stores, and DAPP is proposed to block the K^+-channel in a similar way to ATP during glucose stimulation. Much work is needed to fully assess the relative contribution of any of the proposed signaling pathways involving metabolic coupling factors.

Expanding the minimal model

So far, we have sketched a minimal model of fuel-stimulated insulin release (summarized in Figure 3a,b). There are at least two subsidiary hypotheses that need to be presented to do justice to current research in this field. One is the proposal that metabolic oscillations are essential for glucose-stimulated release and, by extrapolation, any fuel-stimulated release of insulin [22,23] and the other is the contention that β-cells are unable to respond to fuel, including glucose, on their own without priming by hormones or neurotransmitters [24]. These two hypotheses are discussed below.

Metabolic oscillations – an absolute requirement?

There is no doubt that single β-cells and isolated islets can respond in an oscillatory manner to high blood glucose levels. This response pattern is most distinctly observed by microscopic Ca^{2+} imaging of isolated perifused mouse islets stimulated with moderately high glucose levels (Fig. 5). The Ca^{2+} oscillations are paralleled by oscillatory patterns of insulin release. This can be demonstrated using microperifusion and very sensitive assays for insulin [25].

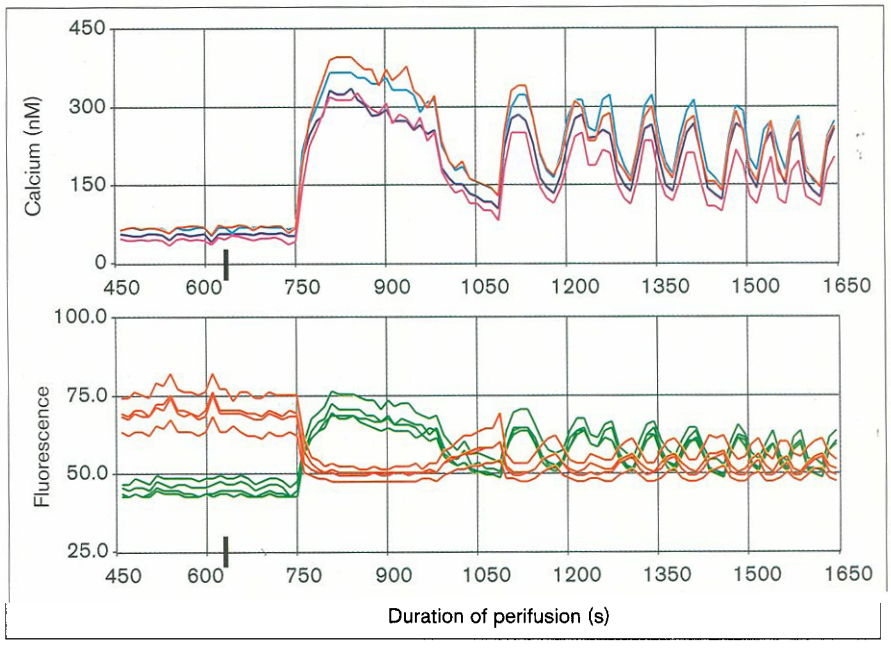
Some investigators believe that these oscillations are primarily an expression of metabolic oscillations resulting from flux control by phosphofructokinase (PFK), which serves as a pulse generator for the glycolytic pathway [22]. It has been shown that islet tissue contains the muscle isoform of PFK; this has kinetic characteristics that allow it to serve as a pulse generator [26]. Most importantly, PFK can be activated by its substrate fructose-1,6-bisphosphate (F-6-P) and by its product, F-1,6-P_2 and its activity can also be positively modified by ADP and negatively modified by ATP. Computer modeling has shown that oscillations in Ca^{2+} concentration may indeed be generated through changes in PFK activity controlled as described above [23]. There is also some experimental evidence to support such a role for PFK [22]. In an oscillatory system, the effects of the periodic changes in the levels of the coupling factors ATP and ADP will be greatly magnified, because the ratio of ATP to ADP reaches the threshold level for triggering insulin release in a pulsatile manner.

If PFK is the metabolic pulse generator that explains the oscillatory response seen for simple cells, intact pancreatic islets and groups of islets, then one must conclude that intra-islet-signaling and inter-islet-signaling systems exist to synchronize the oscillations. It has been suggested that insulin itself may serve as this signal and a mathematical model has been proposed describing how such a system might operate [27].

There is some clinical evidence against this hypothesis, however. Genetic defects of muscle PFK are seen in Tarui's disease, a form of glycogen storage disease, but these defects do not lead to diabetes in humans [28] or dogs [29], as would be expected if the metabolic oscillations suggested to be caused by PFK are essential for insulin release. But it is not yet clear whether patients and animals that lack PFK show pulsatile insulin release. If they do, we propose that it is plausible to assume that the oscillatory release pattern observed in the intact organism is governed by the nervous system [30] or by complex endocrine feedback loops [27] rather than by primary metabolic events of the β-cells governed by PFK.

Figure 5

Synchronized oscillations of calcium in β-cells of the isolated perifused mouse islet stimulated with glucose. Signals of Fura-2-loaded islets were recorded from four quadrants of the islet image. The lower panel shows the records obtained at two wave lengths (green at 334 nm and red at 380 nm) and the upper panel shows the Ca^{2+} levels calculated from the ratio recording data of four defined islet areas (in different colors). The glucose level was 4 mM during preperifusion and 12 mM during stimulation.



Neural and endocrine regulation of insulin release

It is well established that fuel-stimulated insulin release can be markedly influenced by neural and endocrine factors [31]. Acetylcholine, the neurotransmitter of the vagus, strongly potentiates glucose-stimulated insulin release, but is not effective in the absence of glucose. In contrast, the catecholamines adrenaline and noradrenaline block stimulated insulin release. Muscarinic and α-adrenergic receptors mediate these effects of the parasympathetic and sympathetic nervous systems. The biochemical signaling pathways involved in this neuroendocrine modulation of β-cells are, in general, similar to those in other organs.

The secretory response of β-cells to fuel stimulation is also markedly enhanced by the gut hormone glucagon-like peptide 1 (GLP-1) [24], a member of the glucagon family, which is released into the portal circulation when a meal is digested. The physiological importance of GLP-1 is strikingly demonstrated by comparing the stimulatory efficacies of equivalent glucose loads given orally (which induces GLP-1) or intravenously (which does not). Ingested glucose is significantly more effective. Several investigators have gone so far as to suggest that priming by enteric hormones (GLP-1) and/or neural stimulation (vagal acetylcholine) are absolutely necessary for fuels, particularly glucose, to be effective stimuli, suggesting that β-cells are not intrinsically competent as fuel-sensor cells [24].

At least two sets of observations contradict this concept, however. First, a significant fraction of isolated single β-cells studied electrophysiologically, optically and by other approaches show characteristic electrical, ionic and secretory responses when stimulated with high glucose in the absence of neuroendocrine factors, clearly demonstrating their competency [32,33]. Second, various cultured β-cell lines respond to fuels including glucose, amino acids and fatty acids, without prior priming by neurotransmitters and hormones. We therefore continue to believe that considerable subpopulations of β-cells are able to respond to glucose directly, that it is glucose that enables β-cells to respond to other fuels (amino acids and fatty acids), and that the role of transmitters of the autonomic nervous system and enteric hormones is to potentiate or curb the action of fuel molecules, depending on the momentary need of the organism.

Inter-β-cell signaling

A second version of the competency hypothesis states that many β-cells require cell-to-cell contact to respond to fuel stimulation [33]. In this view, only a subpopulation of β-cells are intrinsically competent, and the rest require cell-to-cell contact to achieve the full potential of their insulin secretory response. This view receives some support from experimental evidence that shows a tight synchronization of the pulsatile electrical, ionic and secretory events of thousands of β-cells that constitute a single islet organ (Fig. 5). The synchronization is clearly shown by the microscopic imaging of free Ca^{2+} transients after stimulation with glucose. Ca^{2+} signals recorded from circumscribed separate areas within an islet show a tight synchronization of oscillations. This phenomenon is highly reproducible in isolated mouse islets, and has also been described for isolated human islets but is not readily

demonstrated in islets from rats. The intracellular free Ca^{2+} oscillations or waves have a frequency of about one cycle min^{-1} at 12 mM glucose. Complementary data show that low molecular fluorescent dyes injected into a β-cell spread to microdomains of surrounding β-cells and also that the size of the fields of interconnected cells is greatly increased when glucose levels are high [33].

The structural basis of this phenomenon is found in the form of gap-junctional complexes consisting of the connexin-43 protein which has been intensively studied with the electron microscope and by molecular genetic approaches [33]. The existence of a syncytial arrangement and of synchronization of the secretory responses of cells suggests that recruitment of cells might be necessary so that the threshold for stimulation may be more clearly defined and the dose-response curve can be steeper than possible with the population of disconnected cells. This implies that the thresholds and dose-response curves of individual cells differ widely, which is consistent with experimental data.

It has been suggested that the oscillatory patterns seen in single islets, whatever their origins, are the basis for the much slower pulsations of insulin release from the intact pancreas into the circulation as observed in humans [34]. This is plausible only if all islets are coupled to each other through a comprehensive signaling network that synchronizes the oscillations. Such a network is best conceptualized as neural or hormonal in nature but it remains to be discovered and characterized.

Hyperglycemia, hypoglycemia and chemistry

Diabetes mellitus (hyperglycemia) is a disease that afflicts several hundred million people worldwide and causes severe morbidity and increased mortality; hypoglycemia syndromes, although relatively rare, are hard to manage clinically. Most of the diabetes syndromes have a genetic basis but less than 5% of the genetic defects have been found so far. Examples of defects found in β-cells include mutations of the insulin gene, of the glucokinase glucose sensor gene and of various transcription factors; examples outside the β-cell include defects in the insulin receptor that regulates fuel metabolism of muscle, liver and adipose tissue. Genetic causes of some of the hypoglycemia syndromes have also been identified. In the hypersecreting β-cells, mutations of proteins that are associated with ion channels and mutations of control steps of intermediary metabolism explain the disease. Hypoglycemia syndromes may also arise from mutations of various enzymes of intermediary metabolism unrelated to islet-cell function.

In most of the characterized diabetes mellitus and hypoglycemia syndromes, the pancreatic β-cells are profoundly involved. As outlined here, our understanding of the striking biochemical design features of the pancreatic β-cell has advanced dramatically during the past two decades, making it possible to evolve a plausible general concept of islet-cell function. Many reliable and sophisticated experimental systems are now available to study β-cell function. The stage is thus set for pharmaceutical chemists and pharmacologists to use this new information and technology to attempt to discover chemical compounds that might prevent or remedy some of the recently elucidated β-cell defects. The pancreatic β-cell should therefore be a major target of the pharmaceutical chemical industry.

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