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Secretion of Insulin in Response to Diet and Hormones

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I. The Dual Nature of the Pancreas

The pancreas is a complex gland active in digestion and metabolism through secretion of digestive enzymes from the exocrine portion and hormones from the endocrine portion. The exocrine pancreas, which accounts for more than 95-98% of the pancreas mass (43), is structurally comprised of lobules, with acinar cells surrounding a duct system. The endocrine pancreas makes up only 2% of the pancreatic mass and is organized into the islets of Langerhans— small semi-spherical clusters of about 1500 cells (73) dispersed throughout the pancreatic parenchyme— which produce and secrete hormones critical for glucose homeostasis. The existence of islets was described by Paul Langerhans in 1869, and the functional role of islets in glucose homeostasis was first demonstrated in 1890 when Joseph von Mering and colleagues showed that dogs developed diabetes mellitus following pancreatectomy (22). Though islet mass may vary between individuals— an example is the increase in the setting of adult obesity (83)— the average adult human pancreas is estimated to contain one to two million islets (33, 94). In humans, the concentration of islets is up to two times higher in the tail compared to the head and neck. However, the cellular composition and architectural organization of cell types within the islets is preserved throughout the pancreas (103).

Each pancreatic islet is composed of α, β, δ, ε and PP cells; these are primarily endocrine (hormone-secreting) cells, containing numerous secretory granules with stored hormone molecules, ready for release upon receipt of the appropriate stimulus. Insulin-producing β cells are the most common cell type, making up 50-70% of islet mass, with small islets containing a greater percentage of β-cells in contrast to moderate or large islets (4,5). β cells were first discovered in 1907 by silver staining (50) and were the second islet cell type discovered, thus designated "β"-cells. In addition to insulin, β cells also produce islet amyloid polypeptide (IAPP), or amylin, which is packaged and released within insulin-containing granules (44). Amylin reduces post-prandial hyperglycemia by slowing gastric emptying and promoting satiety.

Glucagon-producing α cells were discovered before β cells, by alcohol fixation, thereby garnering their name "α" –cells (50). As the second most abundant islet cell type, they make up about 35% of islet mass in humans (8) but less in rodents. Glucagon's primary function is to prevent hypoglycemia by stimulating glycogenolysis and hepatic gluconeogenesis (6). Somatostatin-producing δ cells comprise less than 10% of islet mass, and are evenly distributed throughout the pancreas (1). Somatostatin is an inhibitory peptide hormone, inhibiting both endocrine and gastrointestinal hormones. Pancreatic polypeptide

(PP) producing cells, also known as ɣ cells (43, 79), comprise less than 5% of islet mass, and like α cells, are most prominent in the head of the pancreas. PP has roles in exocrine and endocrine secretion functions of the pancreas (107). Ghrelin-producing ε cells are the last discovered islet endocrine cell type. Although present in islets, ghrelin is predominately produced in the stomach; ghrelin suppresses insulin release, and plays a role in regulating energy homeostasis (101).

The close proximity of the acini and the islets of Langerhans mirrors their functional interplay. The anatomic structure of the pancreatic parenchyme allows for a paracrine effect of the islet hormones on adjacent acinar cells, termed the 'islet-acinar' axis (2, 108). Notably, the islets are highly vascularized—receiving 15% of pancreatic arterial blood flow despite composing only 2% of the pancreatic mass (41). Via the islet-acinar portal system, blood bathing the pancreatic islets flows into a capillary bed within the pancreatic acini, thus exposing the acinar pancreas to the islet hormones (66). Insulin binds to an insulin receptor on acinar tissue and potentiates amylase secretion (109). In contrast, somatostatin inhibits pancreatic exocrine secretion (64); endogenous PP is also largely noted to inhibit pancreatic exocrine secretion (90, 107). Studies have been inconsistent with regards to the effect of glucagon, some suggesting a stimulatory effect while many suggesting an inhibitor effect of glucagon on secretion of zymogen granules (2).

II. Insulin Structure

The hormone insulin was first isolated in the 1920's by Dr. Frederick Banting and a medical student Charles Best, garnering Banting (jointly with John James Rickard Macleod) the Nobel Prize in Medicine in 1923. This was a critical step forward in diabetes care, as porcine insulin therapy was then made available for human use to treat type 1 diabetes, an otherwise fatal disease. In the 1950's Frederick Sanger determined its primary amino acid structure, consisting of an A and a B chain connected by disulfide bonds (40, 84). Ten years following this discovery, these chains were found to be from the same polypeptide precursor, preproinsulin. In the 1960's Dorothy Hodgkin defined its tertiary structure. During translation of preproinsulin from its mRNA, the N-terminal signal peptide is cleaved to yield proinsulin. The proinsulin molecule is a single chain polypeptide containing both the A-chain (21 amino acids long) and the B-chain (30 amino acids long). In proinsulin, two chains are connected by C-peptide, which is cleaved to release C-peptide and the remaining insulin molecule, which contains the A- and B-chains connected via two disulfide bonds (40). Although insulin and C-peptide are co-released from β cell secretory vesicles into circulation (81), only insulin is biologically active in regulating blood glucose. C-peptide, however, can serve as a useful clinical and research measure of endogenous insulin production, in patients receiving exogenous insulin injections.

III. Insulin Gene Transcription

The *insulin* gene on chromosome 11 is primarily expressed in pancreatic β cells, but is expressed in low levels in the brain, thymus, and in the yolk sak during fetal development (28, 52, 72). It has three exons and two introns, and its transcription results in the 446 base pair preproinsulin mRNA (**Figure 1**).

Transcription of the *insulin* gene to preproinsulin mRNA is sophisticated and reflects the tight regulation by transcription factors and recruited coactivators. Pdx-1, NeuroD1 and MafA are important transcription factors in β cell function, respond to elevated glucose levels. Individual β cells respond to ambient glucose with differential insulin secretion, and these changes are apparent at the level of gene transcription (16). At the level of the islet, rapid increase in blood glucose results in rapid elevation in preproinsulin mRNA in the endocrine pancreas. A rapid decrease in blood glucose results in a slow decline in preproinsulin mRNA.

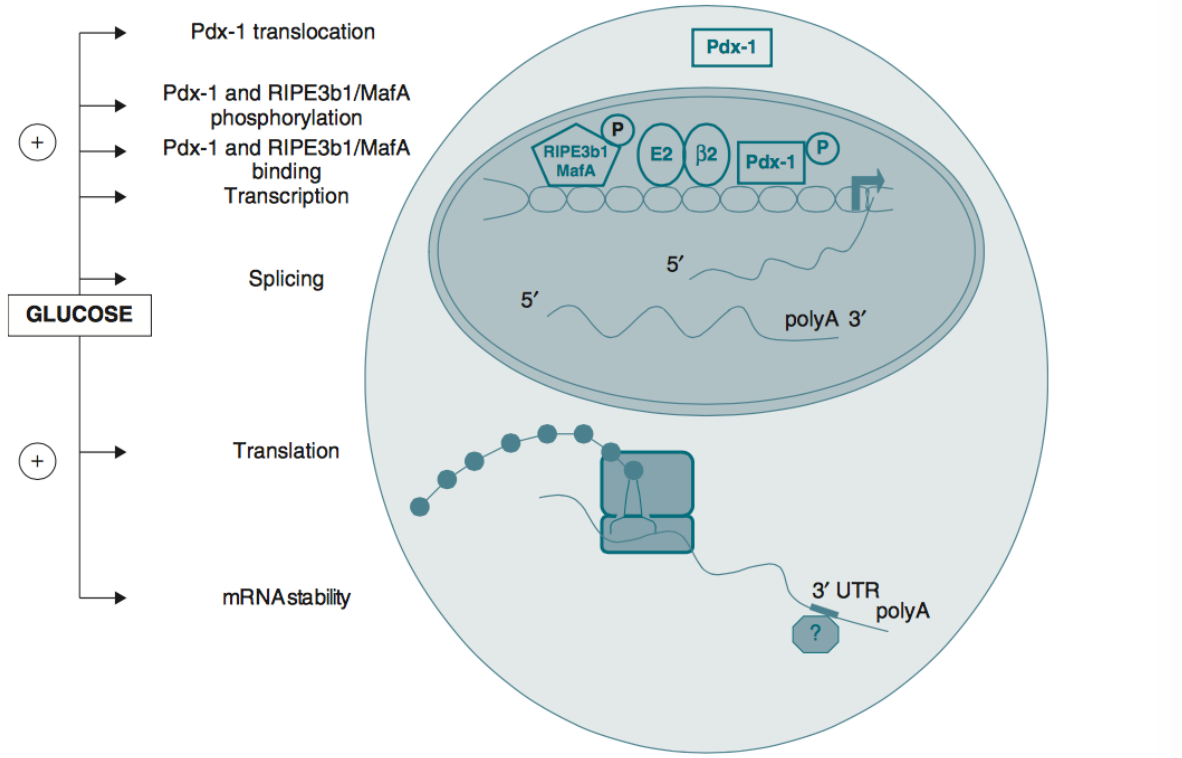

Figure 1. Various levels of glucose regulation of *insulin* gene expression. Glucose stimulates nuclear translocation of Pdx-1; promotes Pdx-1 and MafA phosphorylation and binding to the insulin promoter; and stimulates transcription of the *insulin* gene, pre-mRNA splicing, translation, and mRNA stability. (Used with permission from (74)).

This is due to the unusual stability of preproinsulin mRNA, further stabilized by increased glucose concentrations (25). The specific regulation of this molecule's translation is the primary mechanism of insulin production control (74).

Mature insulin-containing granules are retained from a few hours up to several days within the β cell, ready for transport to plasma membrane and exocytosis when stimulated. The storage of insulin in mature β granules is far greater than that secreted (58, 80). During a 1 hour glucose stimulation only ~1-2% of insulin within a primary islet β cell is released (102). The insulin content within a given β cell remains relatively constant in the short term, but in the long term will adapt in response to physiologic demands (102).

IV. Insulin Function

In an evolutionary milieu of sporadic access to nutrients, insulin became critical in facilitating survival. As an anabolic hormone, insulin controls metabolism of carbohydrates, lipids, and protein. It mediates the availability of energy sources in both fasting and fed states. Insulin promotes energy storage in the fasting state and energy utilization and uptake in the fed state (**Table 1**). In so doing, it maintains serum glucose levels within a narrow physiologic range despite variation in energy intake and expenditure. Insulin acts at extracellular insulin receptors in multiple organ tissues including the liver, muscle, and adipose tissue (43), and its effect depends on interstitial insulin concentration which is influenced by insulin secretion rate from β cells and clearance from circulation (68).

The liver serves as the primary storage site for glucose, accounting for 80% of glucose production in fasting states with the kidney only contributing 20% (18, 96).

Table 1. Endocrine Effects of Insulin

Tissue	Effect of Insulin
Liver	**Catabolic Pathways** Inhibits glycogenolysis Inhibits conversion of fatty acids and amino acids to keto acids Inhibits conversion of amino acids to glucose **Anabolic Pathways** Promotes glucose storage as glycogen (induces glucokinase and glycogen synthase, inhibits phosphorylase) Increases triglyceride synthesis and VLDL formation
Muscle	**Protein Synthesis** Increases amino acid transport Increases ribosomal protein synthesis **Glycogen Synthesis** Increases glucose transport Induces glycogen synthetase Inhibits phosphorylase
Adipose Tissue	**Triglyceride Storage** Lipoprotein lipase is induced by insulin to hydrolyze triglycerides in circulating lipoproteins for delivery of fatty acids to the adipocytes Glucose transport into cell provides glycerol phosphate to permit esterification of fatty acids supplied by lipoprotein transport Intracellular lipase is inhibited by insulin
Brain	**Decreased appetite** **Increased energy expenditure**

(Adapted from Masharani and German (60)).

To preserve glucose stores, the low insulin concentrations in the portal venous blood—as seen in the fasting state-- allows minimal glucose production, only enough to match the needs of essential glucose-dependent tissues including the red blood cells and the central and peripheral nervous systems. The liver also clears insulin more rapidly in the fasting state, thus maintaining low circulating insulin levels. Low insulin concentrations also contribute to lipolysis in adipocytes, releasing free fatty acids to encourage utilization of lipid over glucose to meet resting energy needs. Hepatic glucose release during fasting states through glycogenolysis and gluconeogenesis is stimulated by counter-regulatory, or 'anti-insulin' hormones. Glucagon plays a major role, with synergistic effects from catecholamines, cortisol, and growth hormone (68).

By contrast, in the fed state-- in response to digestion and absorption of nutrients-- circulating insulin concentration increases in the portal vein secondary to insulin secretion from pancreatic β cells. The increased insulin and glucose concentrations normally limit hepatic glucose production and stimulate liver glucose uptake through glycogen deposition (23, 32, 91). Insulin causes upregulation of hexokinase, phosphofructokinase, and glycogen synthase within hepatocytes, thus inhibiting glycogenolysis and gluconeogenesis and stimulating glycogen synthesis (18).

The effect of insulin on gluconeogenesis can be direct (via its effect on the liver) or indirect via its effect on islet α cells (by decreasing glucagon

secretion), adipose tissue (by suppressing lipolysis), skeletal muscle (by reducing proteolysis), and the brain (pleiotropic effect) (32, 65).

In situations when there is poor insulin response such as type 2 diabetes mellitus or insulin resistance, the process of gluconeogenesis continues even in the fed state, thus, further compounding hyperglycemia (32).

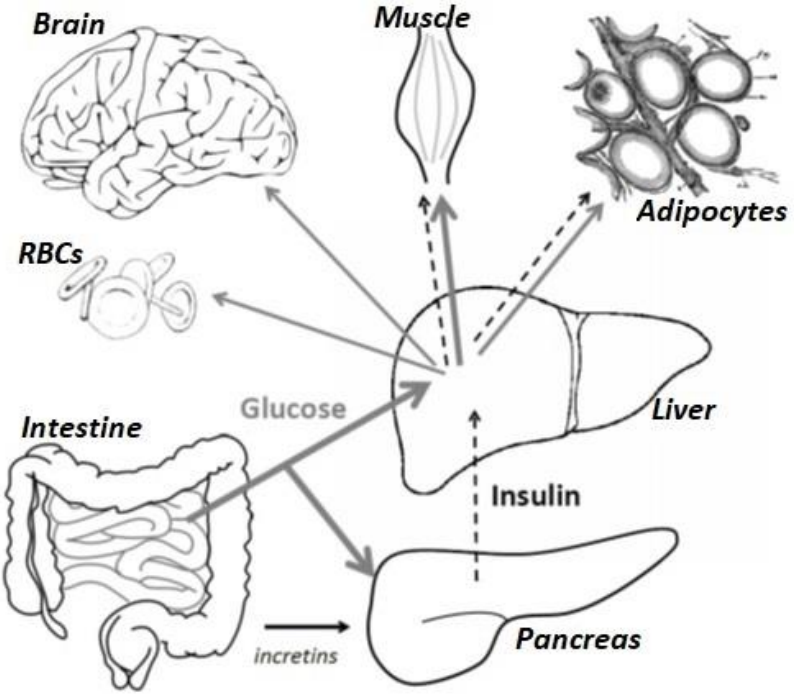

Figure 2. **Glucose homeostasis in the fed state.** Glucose absorbed from the digestive tract enters the portal blood flow and then systemic circulation. In the fed state, increased glucose stimulates insulin release from the pancreatic β-cells. Insulin acts at the level of the liver to inhibit hepatic gluconeogenesis, at the skeletal muscle to promote storage of glucose as glycogen, and in the adipocytes to stimulate lipogenesis. High insulin levels inhibit the release of non-esterified fatty acids. Incretin hormones released from small intestine in response to a meal augment pancreatic glucose-stimulated insulin secretion. Brain and red blood cells take up glucose independently of insulin in the fasting and fed state. In the fasting state (not shown), in the setting of low circulating insulin, hepatic gluconeogenesis, glycogenolysis, and release of non-esterified fatty acids occurs. Solid line stimulation; dashed lines denote inhibition.

Liver clearance of insulin is decreased in the fed state, thus further increasing the circulating insulin concentration. In adipocytes, insulin upregulates lipoprotein lipase and downregulates hormone sensitive lipase, which inhibits lipolysis and subsequent free fatty acid release (29). In hepatocytes, insulin instead stimulates hepatic free fatty acid synthesis from glucose, thereby increasing lipid stores. Proteolysis of skeletal muscle is also inhibited by insulin, which along with lipolysis inhibition, limits delivery of glucose precursors (glycerol and amino acids) to the liver. Systemic circulation of insulin stimulates glucose uptake and utilization in skeletal muscle and adipocytes.

In summary, the release of insulin in the fed state, (1) promotes accumulation of energy stores through glycogenesis and lipogenesis, (2) reduces new hepatic glucose output by preventing glycogenolysis and gluconeogenesis (in the non-insulin resistant, non-diabetic individual), and (3) promotes uptake of glucose by skeletal muscle and fat, the net effect of which is to maintain a normal circulating serum glucose levels while storing extra energy for use during later periods of fasting (**Figure 2**).

Table 2. Most common glucose transporters (GLUT) in human tissues

Glucose Transporter	Insulin sensitivity	Tissue(s)
GLUT-1	Insulin -independent	RBCs; blood brain barrier; more recently identified in human β-cell
GLUT-2	Insulin -independent	β-cell; kidney, liver, intestinal cells
GLUT-3	Insulin -independent	Blood-brain barrier, placenta
GLUT-4	Insulin -dependent	Skeletal muscle, smooth muscle, cardiac muscle, adipocytes

Glucose movement into cells is made possible by specific protein transporters within the plasma membrane of glucose-responsive cells that reversibly bind glucose and transport it bidirectionally across the cell membrane. There are 14 known glucose transporters (GLUTs) (56, 99). They are present in different concentrations and in different tissues, with varying sensitivity to insulin (**Table 2**).

Tissues such as muscle and adipocytes carry the insulin-dependent glucose transporter GLUT-4 and uptake of glucose into these tissues occurs only under conditions of adequate circulating insulin. In contrast, vital organs such as red blood cells, brain, placenta, and kidney carry insulin-independent glucose transporters. Thus, these latter essential organs can continue to function even in states of insulin deficiency. β-cells also depend upon on a glucose-independent transporter, GLUT2, to allow ambient blood glucose to freely transverse the β-cell membrane in order to stimulate insulin production.

V. Insulin Secretory Pathway

The pancreatic β-cells act as a self-contained system to secrete insulin in response to changes in ambient blood glucose concentration, in order to maintain glucose homeostasis. Glucose is freely taken up into the β-cell via GLUT transporters, metabolized to produce ATP, which triggers a cascade of signals within the β cell necessary for glucose-induced insulin secretion. While GLUT2 has been traditionally assumed as the major mediator of glucose uptake into β-cells based on extrapolation from rodent studies and subsequent confirmation of GLUT2 transporters on human β-cells (17, 71, 100), more recent studies in human islets suggest that the other insulin-independent glucose transporters GLUT1 and GLUT3 play a more important role, and are the main glucose transporters in human islet β-cells (3, 98). This redundancy explains why individuals with variants in the gene encoding GLUT2 (SLC2A2 mutations, or Fanconi–Bickel syndrome) do not have significant abnormalities in insulin secretion (89).

As blood glucose increases (e.g., after a meal), there is a resultant flux of glucose across the GLUT transporters in the β-cell. Subsequently, within the β-cell, glucose is phosphorylated to glucose-6-phosphate by glucokinase. This is the rate-limiting step of insulin secretion, and as such, glucokinase is considered the “glucose sensor” for the β-cell (17, 61). Because of this critical role of glucokinase, individuals with heterozygous mutations in the glucokinase gene have a mild to moderate non-progressive hyperglycemia (maturity onset of diabetes in the young, type 2) (12). Once in the mitochondria, glucose-6-phosphate is metabolized by the Krebs cycle to produce ATP. The resultant ATP binds and closes the ATP-dependent potassium channel, a pore across the cell membrane, which consists of four Kir6.2 subunits and has four regulatory SUR (sulfonylurea receptor) subunits. Channel closure blocks potassium exit from the β-cell, thus depolarizing the cell membrane.

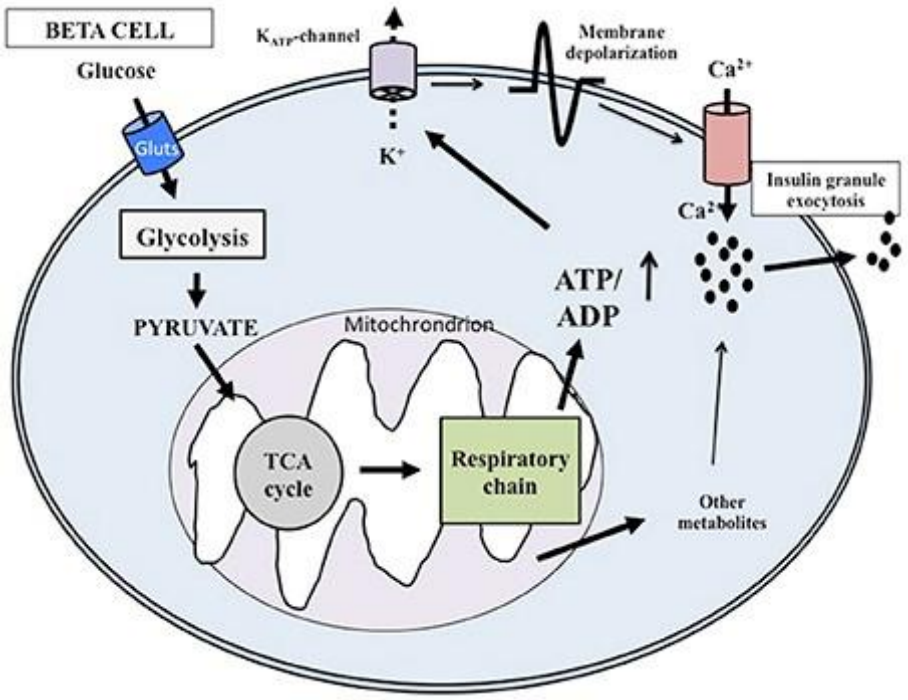

Figure 3. Glucose stimulated insulin-secretion coupling in the β cell. The main pathway of glucose stimulated insulin secretion in the beta cell. Glucose enters the beta cell through GLUT transporters. Glucose metabolism results in an enhanced cytoplasmic ATP/ADP ratio which prompts closure of ATP-sensitive K^+ (K_{ATP}) channels in the plasma membrane evoking membrane depolarization and subsequent opening of voltage-gated Ca^{2+} channels. This culminates in an increase in cellular Ca^{2+} influx- a primary driver of insulin exocytosis. Ca^{2+} and vesicle docking and fusion events can also be modulated by agents acting through the phospholipase C (PLC)/protein kinase C (PKC) or adenylate cyclase (AC)/protein kinase A (PKA) pathways, via neuro-hormonal and metabolic amplification (not illustrated). (Used with permission from (59)).

Once the cell is depolarized, the L-type voltage-gated calcium channels are triggered, increasing influx of calcium and resultant cellular calcium concentrations. Increased cytoplasmic calcium concentrations triggers release of insulin and C-peptide from a pool of insulin-containing docked secretory vesicles and stimulates the migration of additional vesicles to the cell membrane (**Figure 3**). Though simple glucose-stimulated insulin secretion (GSIS) as described above is considered the primary pathway for insulin secretion, the full picture is more nuanced. GSIS is augmented by amplifying pathways including: (1) metabolic amplification by amino acids, free fatty acids, and glucose itself; and (2) neurohormonal amplifiers such as GLP-1 and parasympathetic innervation (14, 34, 48, 76). More recent data from mice suggest a role for skeletal muscle in regulating β-cell insulin secretion via production of an anorexic factor typically derived from the hypothalamus in the brain called BDNF (brain-derived neurotrophic factor) (26). This effect is mediated via the BDNF receptor (TrkB.T1) which is expressed on β-cells, and is thought to play a potential role in exercise-induced glucose metabolism (26). These physiologic, and pharmacologic, triggers for insulin secretion are further described in the following sections. About half of insulin secretion occurs as basal insulin release, while the other half occurs as 'bolus' insulin responses to a meal (62). This basal-bolus dynamic of insulin secretion is important in considering clinical management of the patient with diabetes (**Figure 4**). In those with complete insulin deficiency—e.g. type 1 diabetes, late-stage type 2 diabetes, or late-stage chronic pancreatitis diabetes—insulin analogs are administered by multiple daily injections or a continuous subcutaneous insulin infusion (insulin pump) to mimic this basal-bolus pattern of endogenous insulin secretion.

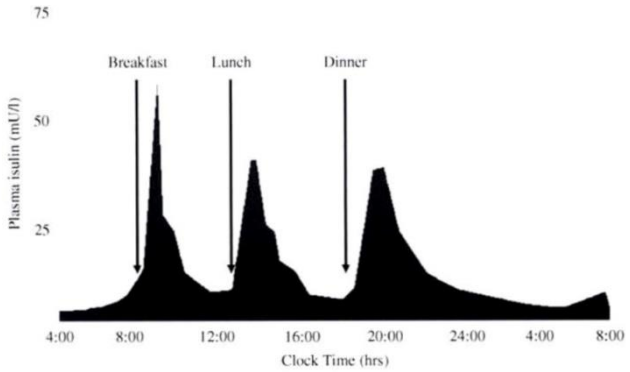

Figure 4. Diagrammatic illustration of insulin secretion. A low background secretion exists upon which is superimposed insulin secretory bursts stimulated by food intake. (Used with permission from Thompson, Christie, and Hindmarsh (97)).

VI. Regulation of Insulin Release

Insulin release from pancreatic β cells is tightly regulated, and allows the sensitive response of insulin levels to calorigenic nutrients in the body. Glucose, free fatty acids, and amino acids serve as fuel stimuli for insulin release, promoting insulin granule exocytosis. Additional hormonal factors influence the regulation pathway. Pharmacological agents can also be used to augment insulin release.

A. Glucose-stimulated insulin secretion

Glucose-stimulated β-cell insulin release is the primary mechanism of insulin regulation (**Figure 3**) (35, 88).In humans, this is illustrated by use of the hyperglycemic clamp technique (**Figure 5**), in which individuals are made rapidly hyperglycemic by injection of intravenous dextrose, and hyperglycemia is maintained by variable rate dextrose infusion at a predefined target glucose (20). Hyperglycemic clamp studies demonstrate a dose-response of insulin secretion in response to glucose concentration, with greater degrees of hyperglycemia eliciting a more robust insulin secretory response in the non-diabetic individual (70, 82). Using this research technique, two distinct phases of insulin secretion are observed. During the first phase insulin response (otherwise referred to as the acute insulin response to glucose, AIRglu), there is an immediate and transient rise in insulin secretion, peaking by five minutes and lasting no more than ten minutes. This first phase of insulin secretion is hypothesized to largely result from the immediate release of insulin from insulin secretory vesicles that are already docked and primed at the β-cell membrane. This first phase response is lost under conditions of diabetes mellitus, when β-cell reserves are exhausted (104). The second sustained phase begins at this ten-minute time-point and lasts as long as the glucose elevation is elevated. The second phase results from recruitment of insulin secretory vesicles to the β-cell membrane, and is also controlled by intracellular calcium levels (68).

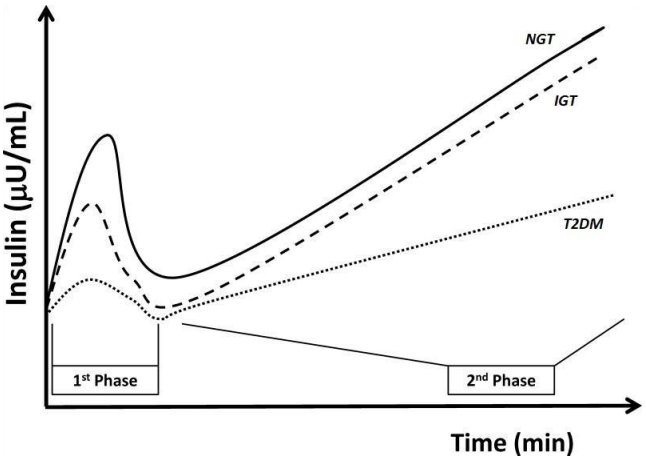

Figure 5. Hyperglycemic clamp illustration. Example of hyperglycemic clamp testing in obese adolescents with normal glucose tolerance (NGT, solid line), impaired glucose tolerance (IGT, dashed line), and type 2 dibetes (T2DM, dotted line). In the hyperglycemic clamp in healthy, non-diabetic individuals, glucose concentration is briskly elevated by administering a suitable intravenous glucose infusion at time 0. This elicits a rapid and short-lived insulin secretion peak (first-phase secretion) due to release of preformed insulin vesicles, followed by a drop towards basal levels and then by a relatively rapid return to a sustained increase in insulin in the second half of the clamp (second-phase secretion) as dextrose infusion is continued. This example illustrates the loss, in first and second phase insulin secretion, as individual progress from normal to impaired glucose tolerance, to type 2 diabetes. In the latter, the first phase insulin response is essentially lost and the second phase insulin response is reduced. (With permission from Wiess et al, (104)).

It is unclear how significant first and second-phase insulin responses are in the 'real world' setting. In contrast to this scenario of rapid infusion of intravenous glucose, ingestion of a physiologic meal results in a much more gradual rise of serum glucose (15). However, characterization of first phase insulin response is critically important in diabetes research. In progression to type 1 and type 2 diabetes mellitus, the earliest abnormality is a loss in the first phase insulin secretion (measured as the AIRglu). Although chronic pancreatitis diabetes is much less studied, this appears likely also to be the case in patients with chronic pancreatitis progressing to diabetes based on limited studies, and often in patients with chronic pancreatitis who have diabetes or pre-diabetes (18). The AIRglu can be elicited experimentally by administering a 0.3 g/kg dextrose bolus and sampling insulin levels at baseline and at +2, 3, 4, 5, 7 and 10 min after the rapid IV administration of dextrose. The AIRglu can be calculated using various methods, including but not limited to the area under the curve minus baseline or mean of the 2-5 min values minus baseline.

Interestingly, glucose also appears to be a 'metabolic amplifier' for insulin secretion, in addition to the classic pathway of glucose-stimulated insulin secretion. Glucose amplifies insulin secretion, a process called time dependent potentiation of insulin secretion—when β-cells are exposed to hyperglycemia this augments subsequent insulin secretory responses to glucose (112).

B. Proteins and Amino Acids

Pancreatic β cells adjust insulin secretion based on other nutrients including amino acids, fatty acids, and ketone bodies. Oral protein intake, and subsequent rise in serum amino acids, stimulate insulin release by direct β cell stimulation (11, 45, 69). The insulinotropic effect varies among amino acids, and there appears to be a synergistic effect of mixed amino acids versus individual administration (24).

Some amino acids stimulate insulin secretion by acting as substrates in the Krebs cycle, metabolizing glucose-6-phosphate to create ATP. Enzymes active in β cell mitochondrial amino acid metabolism have been implicated in hyperinsulinemic hypoglycemic syndromes associated with high-protein containing meals (Prentki, Matschinsky, and Madiraju 2013). The ATP binds to and closes the potassium channel, leading to cell depolarization and insulin secretion. There seems to be a direct effect of proteins and amino acids on β cell glucose sensitivity, because ingestion of amino acids with glucose results in the same plasma insulin concentrations as elicited by a lower level of glucose alone (27).

C. Lipids and Free Fatty Acids

It is generally accepted that lipids play a role in insulin secretion signaling, but the precise pathways and molecules involved in the process remain less well understood. Lipid breakdown and metabolism to signaling molecules has been linked to glucose metabolism through enhanced membrane phospholipid metabolism turnover and other pathways yet to be firmly established. It is thought that free fatty acids (FFA) modulate β-cell insulin secretion either directly via GPR40 (G-protein coupled receptor on the β-cell) leading to insulin secretion, or indirectly via oxidation of FFA to acyl coA, which enters the Krebs cycle and generates ATP (43).

Glucose and FFA metabolism have been shown to be tightly linked and likely includes malonyl-CoA/carnitine palmitoyltransferase I/fatty acyl-CoA metabolic signaling network and the glycerolipid/free fatty acid (GL/FFA) cycle (13, 75). The GL/FFA cycle along with the Krebs cycle and pyruvate cycling are the three likely interlined metabolic cycles that play essential roles in insulin secretion promoted by glucose, FFA, and amino acids (76). In so doing, FFA work synergistically with glucose-stimulated insulin secretion to enhance insulin secretion in nutrient-abundant states.

Chronic elevation of fatty acids may increase basal insulin secretion levels but inhibits glucose-

stimulated insulin secretion. Chain length and degree of saturation affect the role free fatty acids play in regard to insulin plasma levels (95). Adipose tissue responds to insulin resistance with a persistently elevated rate of lipolysis, thus increasing the plasma free fatty acid levels. This is believed to be important in type 2 diabetes development (46).

D. Incretin Hormones

Though glucose concentrations can account for the majority of changes in insulin concentrations, complex studies evaluating *in vivo* insulin concentrations following meals have identified other factors (67). Indeed, insulin secretion following an oral glucose tolerance test is directly related to blood glucose levels, but is considerably higher than predicted following intravenous glucose infusion. These findings suggest a role for potentiating effects on insulin release by hormones that specifically respond to oral glucose, the "incretin effect". This terminology is derived from intestinal hormones called incretins, which are credited with facilitating this response.

The most active incretins are glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) (38, 106), but gastrin, secretin, and cholecystokinin may also have minor roles. In response to glucose and other nutrients, intestinal L cells secrete GLP-1 and K cells secrete GIP. These hormones then bind their specific receptors on the pancreatic β-cell membrane. GLP-1 binds a G protein-coupled receptor. This results in direct activation of *insulin* gene's cyclic-AMP (cAMP) response element (CRE) of the 5'-proximal control sequence (49, 93). It can also augment Pdx-1 binding in the setting of a glucose-stimulus, and stimulate transcription of the PDX-1 gene (39). Finally, it potentiates glucose-induced *insulin* gene transcription by activating NFAT (nuclear factor of activated T-cell) (57). The incretin effect is also mediated by glucose concentration, stimulating more insulin secretion in more extreme hyperglycemic states. GIP and GLP-1 receptors also exist on neuronal cells (e.g. nodose ganglion of the Vagus nerve), suggesting an additional indirect role in β-cell regulation (37). GLP-1 and GIP are cleared by dipeptidyl peptidase-4 (DPP-4) which is present on vascular endothelium. As a result, their half-life iin the circulation is 2-3 minutes and 4-5 minutes, respectively (63).

VII. Insulin's Counterregulatory Hormones

The tight control of energy utilization and stores by insulin is balanced by the counterregulatory hormones glucagon, pancreatic polypeptide, somatostatin, cortisol, catecholamines, and growth hormone. There is asymmetry in the glucose regulation hormones, as insulin is the only hormone to prevent against hyperglycemia, while at least three other hormones (cortisol, glucagon, and adrenaline) prevent hypoglycemia. Collectively, these counter-regulatory hormones act to promote glucose release from the liver by glycogenolysis and gluconeogenesis, and inhibit glucose storage during times of starvation.

Glucagon is formed within pancreatic α islet cells and has a hyperglycemic effect on the body (6). Its name is derived from *glucose agonist* (36). Glucagon carries out its effects via activating its G-protein coupled receptor that is found in various organs/tissues such as the liver, adipose tissue, kidneys, gastrointestinal (GI) tract, brain, and islet α- and β-cells (105). It stimulates glucose production from amino acids and glycerol through gluconeogenesis and from the liver through glycogenolysis. Glucagon also acts at the adipocyte to upregulate hormone-sensitive lipase, thereby enhancing lipolysis and free fatty acid delivery to the liver (54). In the brain it increases satiety (9), and in the GI tract it reduces GI motility (47). Glucagon, via its autocrine role, stimulates further glucagon secretion through its effect on α-cells (55). Interestingly, glucagon stimulates insulin secretion via glucagon's effect on β-cells. It is not clear if this effect is mediated mainly via glucagon's effect on glucagon receptors or on GLP-1

receptors (105). This effect on insulin secretion occurs in the fed state (10).

Mechanisms explaining glucagon secretion are not as well understood as those of insulin secretion, although the direct effect of reduced glucose on cAMP (111), and the sodium-glucose cotransporters (SGLT) are thought to play a role in α-cell glucose transport (3). Mice and human data suggest that α-cell inhibition can occur, at least in part, due to the paracrine action of somatostatin from δ-cells as a result of gap junction-dependent activation by adjacent β-cells (7).

Cortisol antagonizes insulin's function by promoting protein catabolism to provide amino acid substrate for gluconeogenesis and also impairs peripheral insulin-mediated glucose uptake.

Catecholamines directly affect β-cell secretion of insulin, as activation of α-2 inhibits insulin secretion and β stimulation increases it. Catecholamines promote adipocyte lipolysis, hepatic glycogenolysis and peripheral insulin resistance. Epinephrine inhibits insulin secretion through inhibiting the rate of *insulin* gene transcription (110). Somatostatin also destabilizes the preproinsulin mRNA, resulting in premature degradation (72).

Somatostatin is released from pancreatic islet δ cells and exerts inhibitory effect on pancreatic β cells. Once bound to specific somatostatin receptors, β cell membrane repolarization is induced, resulting in reduction of calcium influx and thereby inhibiting insulin release (88, 110).

Pancreatic polypeptide (PP) is secreted by PP, or F, cells in pancreatic islets (107). In addition to its effects reducing gastric acid secretion, decreasing gastric emptying and slowing upper intestinal motility, PP acts within the pancreas to self-regulate pancreatic insulin secretion.

VIII. Pharmacologic Modulators of Insulin Response

There is a plethora of pharmacologic agents designed to target various aspects of glucose metabolism. In this chapter, we provide examples of pharmacologic agents that directly or indirectly modulate insulin response.

A. Incretin mimetics

Diabetes therapeutics have recently utilized the role of incretin hormones for pharmacologic benefit. Due to the desirable effect of GLP-1 on hemoglobin A1c (HbA1c) reduction and weight loss (42), GLP-1 receptor agonists and inhibitors of its degradation via dipeptidyl peptidase-4 (DPP-4) inhibitors, have been used to treat type 2 diabetes since 2005.

Short-acting GLP-1 receptor agonists (such as exenatide and Liraglutide), and long-acting GLP-1 receptor agonists (such as weekly exenatide and Semaglutide) potentiate insulin secretion and reduce gastric motility (31). Given that GLP-1 receptor agonists potentiate glucose-induced insulin gene transcription, they, alone, do not induce hypoglycemia when used as monotherapy (21,79).

DPP-4 inhibitors (such as sitagliptin) can significantly increase the peak post-prandial concentration of GLP-1 (Herman et al. 2006). Additionally, sitagliptin has been found to potentiate GSIS independently of GLP-1 via islet peptide tyrosine tyrosine (PYY) (30).

B. Sulfonylureas

Through a direct action on pancreatic islet cells, sulfonylureas are pharmacological agents that stimulate insulin secretion, thereby lowering blood glucose levels. This class of medication was discovered by happenstance in 1942 when Marcel Janbon, a clinician at the Clinic of the Montpellier Medical School in France found his patients treated for typhoid fever with a new sulfonamide (2254 RP) developed hypoglycemia. Shortly after this, his colleague Professor August Loubatieres established the hypoglycemic property of 2254 RP and its analogues were by direct action on

pancreatic islets. This marked the birth of sulfonylureas for treatment of certain forms of diabetes (57). It was not until 50 years later that the mechanism of action was discovered. Sulfonylurea was found to bind to and block the potassium ATP channel on the β-cell surface, thus depolarizing the membrane and provoking calcium influx, raising intracellular calcium concentration, and triggering insulin secretion (86, 87). Sulfonylurea binding to the sulfonylurea receptor associated with the K-ATP channel stimulates events similar to those in response to glucose stimulation.

Sulfonylureas are also used in the chronic treatment of type 2 diabetes mellitus for both their effects on insulin release and blood glucose reduction. In contrast to acute use of sulfonylureas, chronic use results in improved blood glucose control, but with less rather than more insulin secretion (78). Assessments of its chronic effects are difficult to interpret, given that the magnitude of sulfonylurea stimulation of insulin secretion are multifactorial (53).

C. Insulin Sensitizers

Biguanides (such as metformin) and Thiazolidenediones (such as pioglitazone) improve Hepatic and peripheral (muscle and fat tissue) insulin sensitivity, respectively. Metformin is by far the most widely used pharmacologic agent as first line therapy in patients with type 2 diabetes mellitus. Similar to thiazolidenediones, metformin has an effect on improving peripheral insulin sensitivity in addition to reducing hepatic glucose output. Contrary to thiazolidenediones and sufonylureas, metformin does not cause weight gain, and in fact, it has a modest weight loss effect. When used as monotherapy, metformin does not induce hypoglycemia (85).

D. Diazoxide

Diazoxide is a sulfonamide pharmacological agent used in treatment of hyperinsulinism, insulinoma, and hypoglycemia due to overtreatment with sulfonylureas. It works by opening β cell membrane potassium ATP channels, hyperpolarizing the β cells, thus decreasing intracellular calcium concentration and inhibiting insulin secretion (27).

IX. Conclusion

In conclusion, although the pancreatic islets comprise only a small portion of the pancreas, pancreatic islets play a vital role in our well-being and survival through control of glucose homeostasis. Most critically, loss of insulin production from the pancreatic β-cells, whether due to autoimmune destruction in type 1 diabetes mellitus, exhaustion and genetic predisposition to failure in type 2 diabetes mellitus, or bystander fibrotic destruction in pancreatic exocrine disease, results in diabetes. Insulin secretion is tightly regulated in healthy non-diabetic individuals, with both insulin gene transcription and exocytosis from insulin-containing granules responsive to rises in ambient circulating blood glucose. Other nutrients (protein and lipid) play a smaller role. In contrast, the other pancreatic islet cells, particularly the glucagon-producing α cells, play a key role in glucose counter-regulation to avoid dangerous hypoglycemia.

X. References

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