Endocrine Pancreas

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Abstract

The endocrine pancreas is comprised of the islets of Langerhans which contain beta cells that secrete insulin and amylin, alpha cells that secrete glucagon, delta cells that secrete somatostatin, pancreatic polypeptide cells that secrete pancreatic polypeptide, and epsilon cells that secrete ghrelin. The islets have a complex innervation and capillary network that enables communication and coordination of hormone secretion to regulate glucose and nutrient homeostasis.

Keywords

Islets • beta cell • insulin • alpha cell • glucagon • amylin • ghrelin

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L. Poretsky (ed.), *Principles of Diabetes Mellitus*,
DOI 10.1007/978-3-319-18741-9_3

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Introduction

The endocrine pancreas is comprised of the islets of Langerhans and is functionally separate from the exocrine pancreas. While the exocrine pancreas is responsible for secreting digestive enzymes for nutrient absorption, the endocrine pancreas regulates glucose and nutrient homeostasis and metabolism. Adults have approximately one million islets that constitute 1–2% of pancreatic mass.

The majority (~70%) of islet cells are beta (β)-cells which are located centrally in the islet and are surrounded by alpha (α)-cells, delta (δ)-cells,

Table 1 Islet cell types

Cell type	Percentage of total	Hormone
Alpha (a)	15–20	Glucagon, ghrelin
Beta (β)	65–80	Insulin, amylin
Delta (δ)	3–10	Somatostatin
PP	1	Pancreatic polypeptide
Epsilon (ε)	1	Ghrelin

pancreatic polypeptide (PP) cells, and ε-cells (Table 1).

β-cells secrete insulin and amylin, α-cells secrete glucagon, δ-cells secrete somatostatin, PP cells secrete pancreatic polypeptide, and ε-cells secrete ghrelin. The islets have a rich vascular supply and receive 5–10 times more blood compared to a similar volume of exocrine tissue. This vascular supply enables secreted hormones to access the circulation quickly. The islets have a complex innervation and capillary network, such that all islet cells communicate with each other via gap junctions or paracrine signaling, allowing the islets to integrate the hormonal response and function as a coordinated secretory unit. For example, the central location of β-cells and the direction of blood flood flow from center to periphery allows insulin-secreting cells to exert a tonic inhibitory effect on glucagon-secreting α-cells. Disruption of the balance between insulin and glucagon in controlling glucose homeostasis is a contributing factor to the development of diabetes.

This chapter will discuss the functions of each islet cell's hormones and their roles in glucose and nutrient homeostasis.

Beta Cell

Insulin

Insulin Secretion

Insulin is a 51-amino acid peptide that is synthesized within the β-cells of the islets. Preproinsulin is synthesized in the rough endoplasmic reticulum of β-cells and is quickly cleaved to proinsulin, which is transported to the Golgi apparatus for packaging in secretory granules. Clathrin-coated vesicles containing proinsulin can fuse directly with the cell membrane prior to vesicle maturation (constitutive pathway) or can fuse with endosomes before release (constitutive-like pathway) (Fig. 1). However, only a small amount (less than 10%) of proinsulin is secreted unregulated through these pathways; most proinsulin will follow the secretory pathway, where proinsulin is converted to insulin and C-peptide by cleavage enzymes [1]. The secretory granules then fuse with the cell membrane, and insulin and C-peptide are exocytosed in equimolar amounts, making C-peptide a useful marker of endogenous insulin secretion.

After it was discovered that C-peptide had no insulin-like activity, it was presumed to have no biological activity. However, in the past 20 years, research has shown that C-peptide not only has biological activity but may have beneficial effects in improving microvascular complications of type 1 diabetes. C-peptide binds to cell membranes, resulting in increases of intracellular calcium concentrations and activation of nitric oxide synthase in endothelial cells, leading to nitric oxide release [2]. There is also evidence of a direct relationship between C-peptide levels and sodium, potassium-ATPase activity: sodium, potassium-ATPase activity is reduced proportionally to the reduction in C-peptide level, and C-peptide stimulates sodium, potassium-ATPase activity [3]. C-peptide has also been shown to have anti-inflammatory and antioxidant activity, by mediating a negative effect on the nuclear factor kappa β pathway, and a reduction in reactive oxygen species [4]. C-peptide also downregulates expression of VEGF [5], TGF-β [6], PAI-1 [7], ICAM, and VCAM [8]. In clinical studies, treatment with C-peptide improved symptoms of sensory neuropathy and vibration perception [9, 10], and reduced albuminuria excretion and glomerular hyperfiltration in patients with early nephropathy [11]. In streptozoticin diabetic rats, C-peptide prevented retinal vascular leakage [5, 12]. Thus, treatment with C-peptide shows promise as a therapeutic approach for type 1 diabetes; however, more research is needed to identify its cell membrane receptor and its normal physiological role.

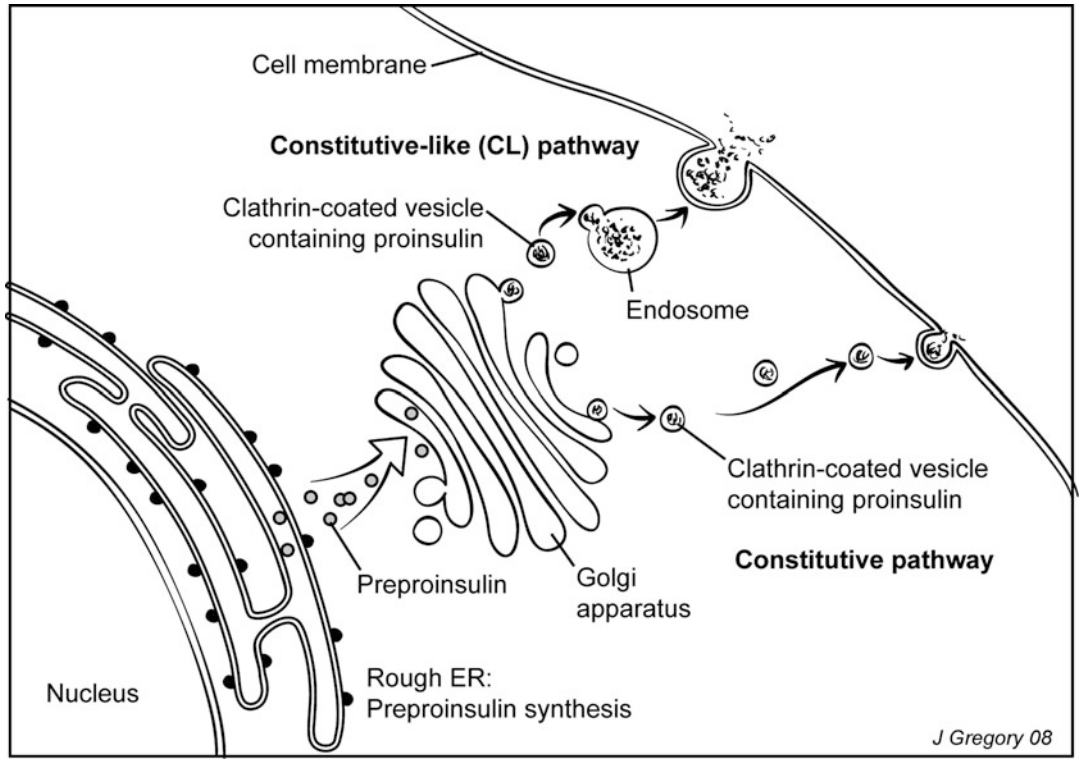

Fig. 1 Insulin biosynthesis and secretion

The total amount of insulin secreted at any given time reflects the sum of the insulin secreted by individual islets. Glucose is the main regulator of insulin secretion. Increases in glucose, either due to an ingested meal or intravenous glucose, lead to a rapid release of insulin that lasts about 10 min – the first phase insulin response. The second phase insulin response is a prolonged plateau of insulin secretion (from both stored insulin and newly synthesized insulin) that lasts as long as the blood glucose remains elevated. In type 2 diabetes, the first phase insulin response, to both oral and intravenous glucose, is lost early in the disease, indicating beta cell dysfunction. However, in the same subjects with diabetes, the first phase response to iv arginine is intact, demonstrating that the loss of glucose-stimulated first phase insulin secretion is due to failure to transduce a glucose-associated signal. Sustained levels of high glucose stimulation result in a reversible desensitization of the beta cell response to glucose ("glucose toxicity"), but not to other stimuli.

Insulin is secreted at a rate that depends partly on the blood concentration of glucose. The "fuel hypothesis" states that the intracellular glucose concentration determines the rate of glucose metabolism, and the rate of glucose metabolism determines the rate of insulin secretion (Fig. 2) [13].

Metabolism of glucose increases the ATP: ADP ratio. ATP interacts with ATP-dependent potassium channels to close the channels, leading to depolarization of the membrane potential and opening voltage-gated calcium channels. The cytoplasmic calcium concentration rises, resulting in activation of protein kinases, fusion of insulin secretory granules to the cell membrane, and exocytosis of insulin, i.e., insulin secretion. First phase insulin response is due to immediate release of insulin secretory vesicles

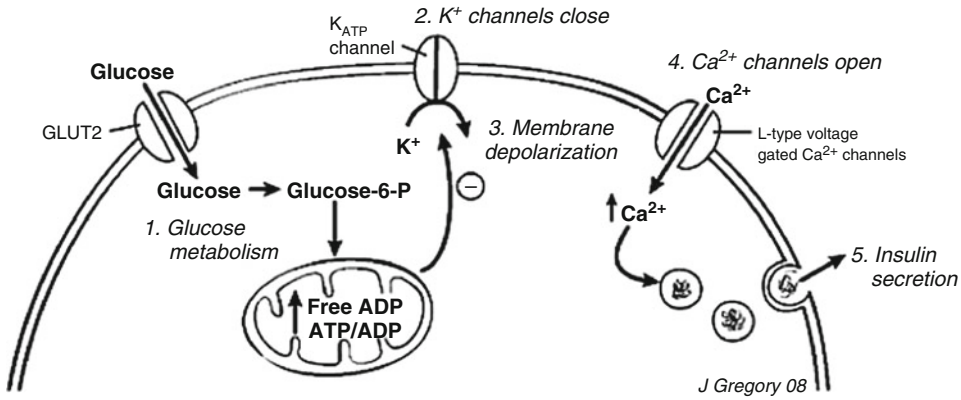

Fig. 2 Schematic View of fuel hypothesis

that are "docked" and "primed" at the β-cell membrane, awaiting glucose-dependent calcium signal, while the second phase represents replenishment of exocytosis-competent secretory vesicles.

Sulfonylureas are able to bind to receptors on the potassium-ATP channels, causing closure of the channels and increasing insulin release. Transgenic mice whose potassium-ATP channels have reduced sensitivity to ATP (and thus channels are not able to close) develop hypoinsulinemia, severe hyperglycemia, and ketoacidosis shortly after birth [14]. Mutations in the sulfonylurea receptor gene (SUR1) or the Kir6.2 gene that encodes the potassium channel subunit have been identified in causing neonatal diabetes mellitus. Treatment with high-dose sulfonylureas in these patients will improve glycemic control, as sulfonylureas will still close the mutated potassium-ATP channels [15, 16].

Glucose enters the β-cell through glucose transporters, GLUT2, which are constitutively expressed on the plasma membranes of islets. Chronic exposure to hyperglycemia increases GLUT2 expression. Glucokinase phosphorylates glucose to glucose-6-phosphate in the rate-limiting step in glycolysis. Thus, since insulin secretion is proportional to the rate of glucose metabolism, which is determined by the actions of GLUT2 and glucokinase, their combined actions form a physiological "glucose sensor." Mutations in the glucokinase gene can cause either hyperglycemia or hypoglycemia by altering the rate of glucose metabolism. Heterozygous mutation of the glucokinase gene results in one of the forms of mature-onset diabetes of the young (MODY2) [17].

Other factors regulating insulin secretion include surrounding nutrients (free fatty acids, amino acids), endocrine hormonal inputs (e.g., glucagon), neural activity within the islets, and interactions between the islets.

Nutrients and Insulin Secretion

The principal role of the pancreatic hormones is to regulate the uptake and release of metabolic fuels from hormone-sensitive tissues, liver, muscle, and fat. Insulin secretion is stimulated after meals, when nutrient levels in the blood are high. Glucagon secretion is inhibited, and high insulin:glucagon ratio promotes nutrient storage. During fasting, when stored fuel energy is needed, insulin secretion is inhibited, glucagon secretion is stimulated, and low insulin:glucagon ratio promotes nutrient release from storage.

Lipids and Insulin Secretion

Free fatty acids, also known as nonesterified fatty acids, are an important energy source for many tissues of the body. In addition, they are metabolized in β-cells where they also serve as important signaling molecules regulating β-cell function. Acute exposure to free fatty acids increases both basal and glucose-stimulated insulin secretion.

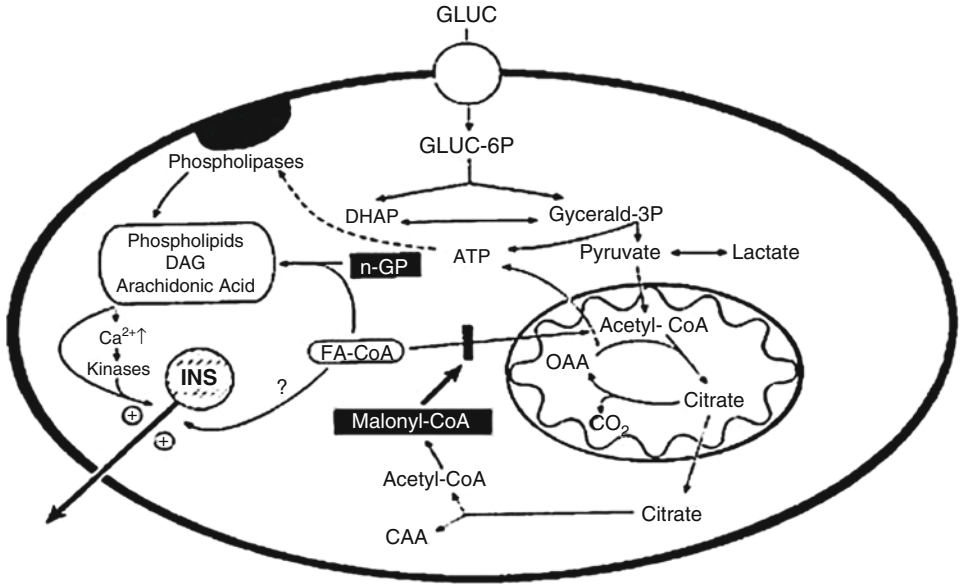

Fig. 3 Malonyl-CoA inhibits CPT-I leading to rise in cytoplasmic fatty acyl-CoA available to enhance insulin secretion [13]

However, chronically elevated free fatty acid levels, as seen in patients with type 2 diabetes mellitus, may have deleterious effects on β -cell function and contribute to β -cell dysfunction and insulin resistance [18].

High glucose and insulin levels lead to Krebs cycle activation, resulting in increased citrate and acetyl-CoA, which are converted to malonyl-CoA via acetyl-CoA carboxylase. Malonyl-CoA is a potent inhibitor of carnitine palmitoyltrasnferase-I (CPT-I), the outer mitochondrial membrane enzyme that transports fatty acyl-CoA into the mitochondria, thereby playing a central role in the balance between mitochondrial glucose and fatty acid metabolism. CPT-I inhibition leads to an increase in cytoplasmic fatty acyl-CoA, which ultimately increases insulin secretion (Fig. 3).

The accumulation of lipids in muscle leads to insulin resistance [19]. Insulin resistance is defined as impaired insulin-stimulated glucose disposal. Obese subjects who are insulin resistant require higher concentrations of insulin to maintain normoglycemia. Insulin-resistant individuals who have beta cell dysfunction and are unable to attain the compensatory insulin response will develop hyperglycemia and type 2 diabetes.

Neural Regulation of Insulin Secretion

The islets are richly innervated by autonomic and sensory nerves. Insulin secretion is enhanced by stimulation of parasympathetic nerves and inhibited by sympathetic nerve stimulation. Sensory pathways are generally inhibitory. Additional neural pathways mediate direct enteropancreatic interactions.

The first phase insulin response, also known as the cephalic phase of insulin secretion, is triggered by the sight, smell, and anticipation of food. This phase is abolished by vagotomy or by ganglionic blockade with muscarinic antagonists, demonstrating that it is mediated by cholinergic neurons of the parasympathetic system. Administration of trimethaphan, a ganglionic blocker, leads to reduction of insulin response and consequently postprandial hyperglycemia at 25–60 min after meal ingestion [19]. Conversely, giving a small amount of insulin in the first 15 min of meal ingestion improves glucose tolerance.

Insulin secretion from the pancreas is pulsatile, suggesting synchronization between the islets. Blocking pancreatic ganglia abolishes this synchronization. Individuals with impaired glucose tolerance and type 2 diabetes lack oscillatory

insulin secretion, suggesting its clinical importance.

The parasympathetic nerves innervating the islets originate in the dorsal motor nucleus of the vagus. Preganglionic fibers traverse the vagus in the bulbar outflow tract and the hepatic and gastric branches of the vagus. They enter the pancreas and terminate in intrapancreatic ganglia, from which postganglionic fibers emerge to innervate the islets. Postganglionic nerve terminals contain acetycholine, gastrin-releasing peptide (GRP), vasoactive intestinal polypeptide (VIP), and pituitary adenylate cyclase-activating polypeptide (PACAP), which bind to their respective G protein-coupled receptors, ultimately leading to increased levels of cAMP and phospholipase activation [20]. Vagal activation stimulates insulin secretion. Stimulation of postganglionic fibers releases acetylcholine, which binds to M3 muscarinic receptors on islet cells.

At times of physiological stress (such as prolonged fasting, exercise, hypoglycemia, hypovolemia), maintaining blood glucose levels becomes vitally important. Glucose output by the liver plays the main role, stimulated in part by the counterregulatory hormones cortisol, epinephrine, and growth hormone. In addition, activation of local sympathetic nerves stimulates glucagon secretion, and concurrently inhibits insulin secretion. The decreased insulin:glucagon ratio triggers hepatic glucose production and output.

The adrenergic nerves innervating the islets originate from the hypothalamus and its postganglionic fibers and are derived from the celiac ganglion and paravertebral sympathetic ganglia. Postganglionic nerve terminals contain norepinephrine, galanin, and neuropeptide Y (NPY). Norepinephrine-induced inhibition of insulin secretion is mediated via α2-adrenoreceptor activation leading to hyperpolarization of the β-cell through opening of the ATP-dependent potassium channels. This prevents the increase in intracellular calcium that is needed for exocytosis of insulin-secretory granules. In addition, there is inhibition of cAMP formation [21].

The islets are also innervated by sensory afferent nerves containing calcitonin gene-related peptide (CGRP) and substance P. CGRP has an inhibitory effect on insulin secretion that is mediated by a reduction in islet cAMP, which probably reflects α2-adrenoreceptor activation. CGRP also stimulates glucagon secretion. The actions of substance P in the islets are not well known, with both stimulatory and inhibitory effects reported. Other nerves that innervate the islets include neurons that contain nitric oxide synthase and cholecystokinin (CCK), both of which stimulate insulin secretion. In addition, nerves originating in the duodenal ganglia directly innervate islets and probably play roles in enteropancreatic neural mechanisms.

Intracellular Pathways and Insulin Secretion

Neurotransmitters and hormones bind to specific cell surface receptors activating second messenger systems that regulate insulin secretion. As mentioned above, binding of VIP, PACAP, GLP-1, and GIP to their respective G protein-coupled receptors generates cAMP and magnifies insulin secretion. Conversely, norepinephrine binding to its inhibitory G protein-coupled receptor inhibits cAMP formation and ultimately insulin secretion.

Cyclic AMP increases intracellular calcium both directly, by activating L-type calcium channels, and indirectly, by activating protein kinase A, which phosphorylates and closes potassium channels that depolarize the plasma membrane potential. In addition, cAMP sensitizes the insulin-secretory machinery by shifting the dose-response curve of calcium–induced insulin secretion to lower calcium concentrations. Protein kinase A also rapidly phosphorylates a set of proteins that potentiate insulin secretion. Finally, cAMP stimulates insulin gene transcription both directly, by binding to a cAMP response element of the insulin promoter, and indirectly, by phosphorylating a cAMP response element-binding protein (Fig. 4).

Three phospholipases in β-cells play roles in regulating insulin secretion: phospholipase A_2, C, and D. Phospholipase C activation from acetylcholine binding to its G protein-coupled receptor hydrolyzes membrane-bound phospholipids to inositol triphosphate (IP_3) and diacylglycerol

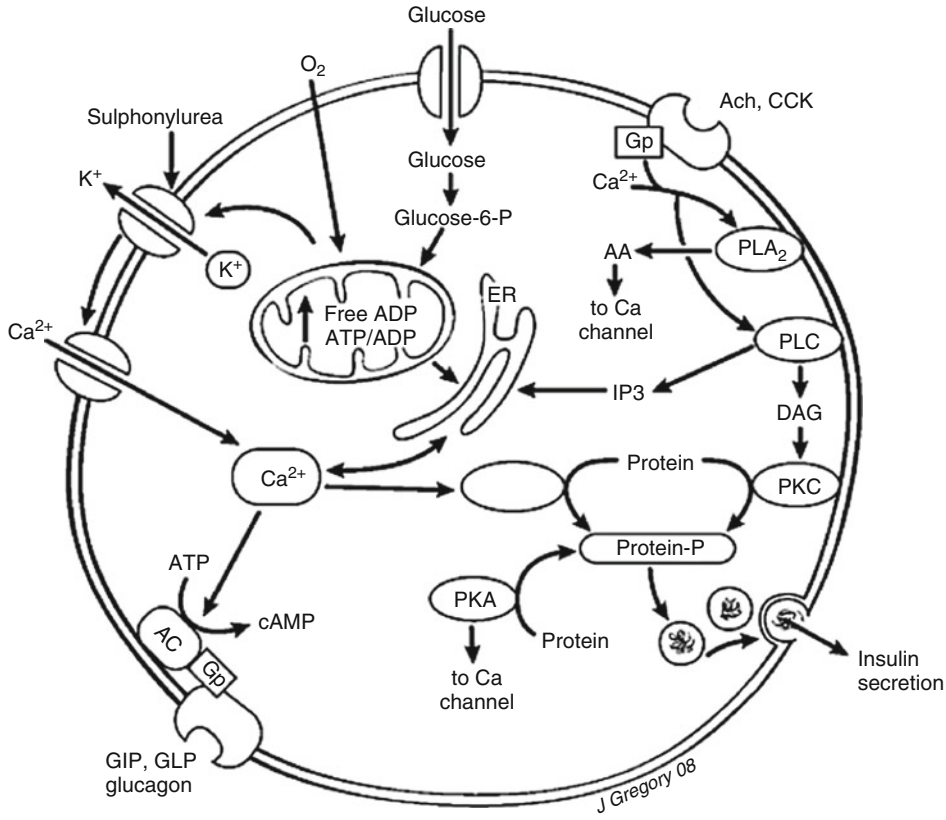

Fig. 4 Intracellular pathways involved in insulin secretion [22]

(DAG). IP_3 then signals intracellular stores of calcium to be released. DAG-activated protein kinase C phosphorylates proteins that ultimately amplify glucose-stimulated insulin secretion. DAG also increases the pool of insulin-secretory granules that can be exocytosed and activates DAG lipase, which liberates arachidonic acid from phospholipids. Arachidonic acid amplifies insulin secretion by increasing voltage-dependent calcium entry, as well as by mobilizing calcium from intracellular stores via protein kinase C.

Amylin

Amylin, also known as islet amyloid polypeptide, is a 37 amino-acid peptide hormone that was discovered in 1986 as a major component of islet amyloid deposits. Amylin is cosecreted with insulin by β-cells in a 15:1 ratio (insulin:amylin). Its secretion is stimulated by glucose, arginine, and free fatty acids. Amylin levels increase after a meal, while fasting decreases its levels. Major effects of amylin include suppression of glucagon, reduction of blood glucose, reduction in food intake, and slowed gastric emptying (Fig. 5).

Amylin receptors are closely related to calcitonin receptors, as they consist of a complex of the calcitonin receptor and a receptor activity-modifying protein (RAMP). There are three types of RAMPs and several splice variants of the calcitonin receptor, leading to many possible amylin receptor subtypes. Amylin binding sites are present in the lung, stomach, spleen, and brain, especially the brainstem. Amylin, with leptin, has been shown to overcome leptin resistance and reduce food intake in obese rats [24].

Pramlintide is a synthetic analogue of amylin that is as potent as human amylin, and has been developed and studied as an agent for type 1 and

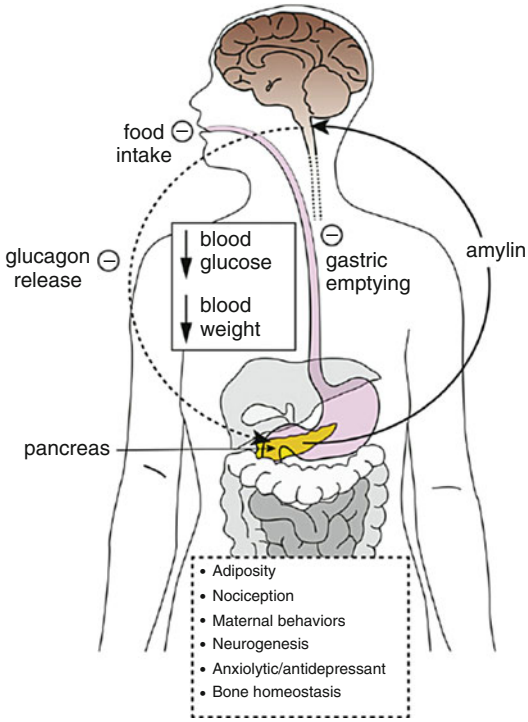

Fig. 5 Major actions of amylin [23]

type 2 diabetes and obesity. Though most of amylin research is focused on food intake and weight regulation, amylin is also being studied in Alzheimer's disease. Lower levels of amylin are found in patients with Alzheimer's disease, and administration of amylin or pramlintide to animals showed improvement in learning and memory, decreased markers of inflammation, and increased markers of synaptic formation [25].

Alpha Cell

Glucagon

Glucagon is synthesized in α -cells and is derived from a large precursor prohormone, preproglucagon, which is cleaved by specific prohormone convertase enzymes, yielding biologically active hormones. In α-cells, prohormone convertase 2 cleaves preproglucagon, resulting in glucagon and a major proglucagon fragment. In L-cells in the intestine, prohormone convertase 1 cleaves the prohormone, resulting in formation of GLP-1 and GLP-2. Additional peptides derived from preproglucagon include glicentin and oxyntomodulin (Fig. 6).

Glucagon was discovered in 1923 [26] when transient hyperglycemia was initially observed after crude pancreatic extracts (that were contaminated with glucagon) were given to animals. The name glucagon was abbreviated from "glucose agonist." Glucagon secretion is stimulated by hypoglycemia and suppressed by hyperglycemia, and thus plays a central role in the maintenance of blood glucose concentrations. Glucagon levels rise with fasting and exercise. During hypoglycemia, insulin levels are low, releasing glucagon from tonic suppression, and glucagon is one of the first hormones secreted in response to falling glucose concentrations. Other counterregulatory hormones, such as catecholamines and cortisol, also play roles in increasing glucose concentrations in response to hypoglycemia. Additional positive regulators of glucagon include sympathetic nerve stimulation, CCK, and GIP, while inhibitors of glucagon secretion include somatostatin, hyperglycemia, and increased levels of fatty acids (Table 2).

The main site of glucagon action is the liver, where glucagon binds to its G-protein coupled receptors on hepatocytes, leading to production of cAMP via adenylate cyclase. This leads to activation of protein kinase A, phosphorylase kinase, and phosphorylase. The result is stimulation of gluconeogenesis and glycogenolysis and inhibition of glycolysis, to increase hepatic glucose output (Fig. 7) [27].

Glucagon also regulates lipid metabolism; in adipocytes, glucagon acts via increased cAMP to stimulate lipolysis, while inhibiting glucose uptake, thereby decreasing triglyceride synthesis. Glucagon also stimulates hepatic fatty acid oxidation [28].

While diabetes was initially considered to be a disease of solely insulin deficiency, it is now accepted that disruption of glucagon secretion (namely excess) is a contributing factor to the development of diabetes. In both type 1 and type

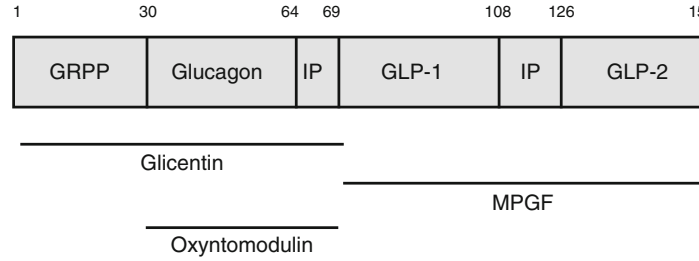

Fig. 6 Structure of Preproglucagon

Table 2 Major regulators of glucagon secretion

Stimulators	Inhibitors
Decreased plasma glucose levels	Elevated plasma glucose levels
Catecholamines	Insulin[c]
Gastrin	Somatostain[c]
Cholecystokinin	Increased levels of circulating fatty acids
Gastric inhibitory polyeptide	Gamma-aminobutyric acid (GABA)
Amino acids (such as: arginine[a], alanine[b], cysteine[b], serine[b], glycine[b])	
Glucocorticoids	
Pituitary adenylate cyclase activating peptide (PACAP) [32]	
Sympathetic and parasympathetic stimulation	

[a]Stimulates both glucagon and insulin release
[b]Stimulates mainly glucagon release
[c]Direct inhibition of a cells

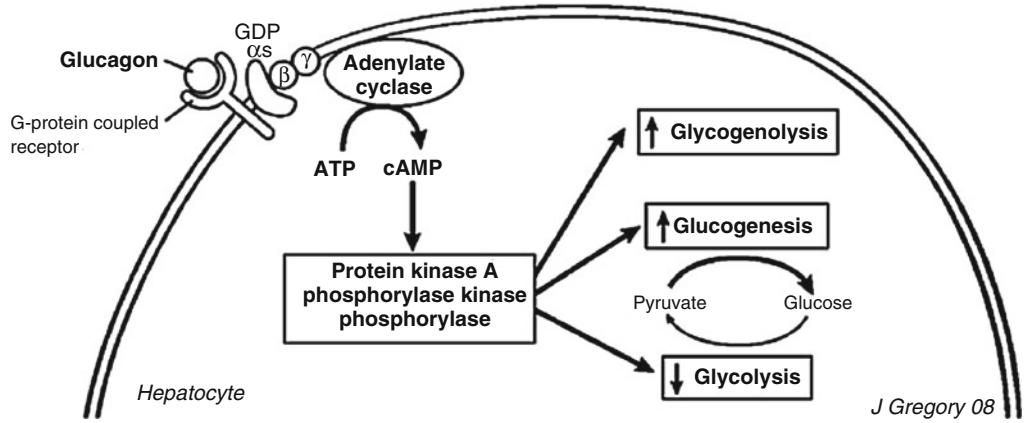

Fig. 7 Mechanism of Glucagon action

2 diabetes, there is chronic hyperglucagonemia despite hyperglycemia that contributes to both fasting and postprandial hyperglycemia. In addition, there is an impaired glucagon response to hypoglycemia, the mechanisms of which are not known, but can have dangerous consequences. α -cell mass is increased in both type 1 and type 2 diabetes, and α-cell archtitecture is also altered, which presumably affects islet communication and contributes to abnormal glucagon secretion [29].

Glucagon-Like Peptides

As mentioned above, GLP hormones are derived from the same preproglucagon gene that yields glucagon, via a different cleavage enzyme, PC1, that is present in L-cells in the intestine. GLP-1 is the major GLP to consider. GLP-1 belongs to a class of incretin hormones, which are responsible for 70% of insulin response to an oral glucose load. Its actions include stimulating insulin secretion, reducing glucagon secretion, promoting satiety, and delaying gastric emptying, all of which are desirable characteristics for a diabetes agent. Its half-life is short (few minutes) due to rapid degradation by dipeptidyl peptidase-4 (DPP-4) enzyme, and prolonging GLP-1 action by either inhibiting DPP-4 or by creating an agonist resistant to degradation has become attractive targets for diabetes agents.

Delta Cell

Somatostatin

Delta cells comprise 5–10% of islet cell volume and secrete somatostatin. Actions of somatostatin include inhibiting gastric hormones (such as gastrin, CCK, secretin, GIP), inhibiting glucagon and insulin, and decreasing the rate of gastric emptying. Its concentration in the blood increases after meals, as a consequence of both gastrointestinal and pancreatic secretions. Intravenous administration of somatostatin inhibits insulin secretion, as well as exocrine pancreatic secretion. However, the precise role of somatostatin in islet function has not been determined. Somatostatin receptors are present on islet β and α cells, suggesting that somatostatin may have a direct role in regulating insulin and glucagon secretion.

In the anterior pituitary, somatostatin inhibits release of growth hormone, thyroid stimulating hormone, and prolactin. Somatostatin and its receptors are found in all neuroendocrine tissues, as well as in the central and peripheral nervous systems. The somatostatin gene encodes two biologically active peptides, named somatostatin-14 and somatostatin-28, reflecting the number of amino acids present. In islets, δ-cells release mostly somatostatin-14, while intestinal cells release somatostatin-28. In addition to acting as hormones, these peptides act as neurotransmitters, neuromodulators, and local paracrine regulators. Their diverse physiological actions include modulation of islet hormone secretion, neurotransmission, smooth muscle contractility, and cell proliferation [29].

PP Cell

Pancreatic Polypeptide

PP cells are mostly located ventrally in the islets, with scattered, individual cells containing PP in exocrine tissue. PP is secreted in response to food intake, with levels increasing 100% above baseline during tasting or chewing food. Its main action appears to be reducing gastric emptying and motility which leads to delaying insulin secretion. In addition to a gastric stimulus, PP is also under vagal regulation; its secretion is stimulated by cholinergic agents and inhibited by anticholinergic agents. Thus, PP cells play an important role in the "gut-brain" axis [30].

Epsilon Cell

Ghrelin

Epsilon cells originate from neurogenin3 (ngn3)-expressing precursor cells, which are common to the other four islet cell types. Epsilon cells comprise up to 30% of islet cells during gestation, but are reduced to less than 5% at birth, and less than 1% in the adult pancreas [31]. Epsilon cells produce only ghrelin, however the main source of ghrelin production is the stomach. Ghrelin is a 28 peptide hormone that was originally found in rat stomach as an endogenous ligand for growth hormone secretagogue receptor, and its name is derived from the Proto-Indo-European word root "ghre" meaning "to grow" [32]. Ghrelin receptors are mainly expressed in hypothalamus, pituitary, first trimester human placenta, and germ cells.

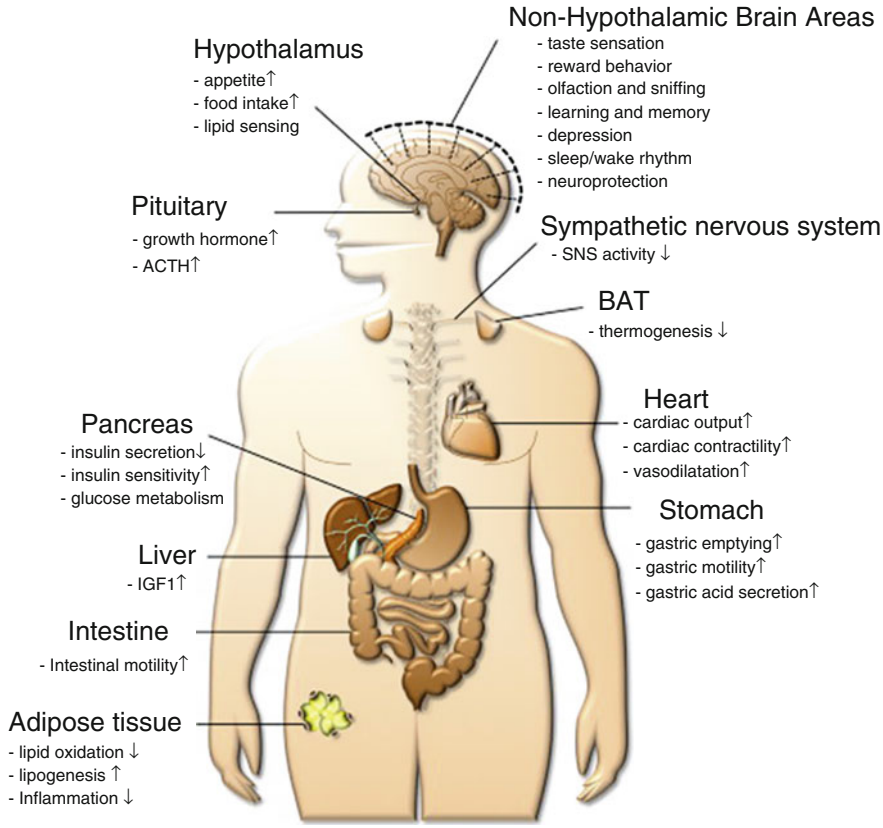

Fig. 8 Physiologic effects of ghrelin [33]

Ghrelin, however, also has actions in nonhypothalamic brain areas, adipose tissue, and the heart (Fig. 8).

Ghrelin stimulates appetite, and its concentration is increased during fasting and reduced after eating, giving ghrelin its nickname as the "hunger hormone" However, the actions and effects of ghrelin are much more complex than its effect on food intake. Other reported effects of ghrelin include regulation of glucose metabolism (decreases insulin secretion), suppression of brown fat metabolism (and increasing lipogenesis), modulation of sleep and stress, and improvements in cardiac function (vasodilatation, cardiac output) [33]. Ghrelin levels are lower in obese and insulin-resistant subjects and higher in patients with weight loss due to exercise or anorexia. Patients who undergo bariatric surgical procedures (Roux-en-Y, sleeve gastrectomy, gastric banding) have lower levels of ghrelin, which is thought to contribute to the weight-reducing effect and success of the procedure [34].

The role of ghrelin within the pancreas is not known; one hypothesis is that ghrelin is important for islet development and growth, given its abundance in the fetal pancreas [33].

Islet Cell Transplantation, Future Directions

While islet transplantation was first successfully performed to correct hyperglycemia in diabetic mice in the 1970s, islet cell transplantation in human subjects did not occur until the 1990s, after improved methods to isolate and purify large quantities of islets were developed. However, islet cell transplantation in the 1990s were

performed with a low success rate (9%). In 2000, the Edmonton Protocol [35] reported successful islet cell transplantation in seven patients, each of whom received islets from two donors, followed by steroid-free immunosuppressive therapy. Long-term follow-up reported that all patients demonstrated islet cell function (measured by C-peptide) though three patients received an additional islet transplant [36]. The Collaborative Islet Transplant Registry (CITR) reported 44% of transplant recipients (of 677 total islet transplants) were insulin independent at 3 years post transplant, from 2007 to 2010, compared to 27% in 1999–2002.

Islet donor availability is one of the main reasons limiting islet transplantation. Transplanted islet mass requires two or more donors, and the amount of pancreatic mass transplanted does not correlate with graft function due to variable loss of functioning islets during the transplantation procedure. Isolating islets from exocrine pancreas tissue without damaging them and culturing islets are challenging processes. Islets require abundant vasculature, especially in the immediate post-transplant state. Transplantation into the liver provides the needed vascular supply, however oxygen tension is not as optimal as in the pancreas, and it is estimated that 50% or more of transplanted islets do not survive transplantation [37]. Another obstacle to islet transplantation is the need for lifelong immunosuppressant therapy to prevent graft rejection and also future autoimmune attack on the transplanted β-cells.

Islet cell transplantation can be considered for patients with type 1 diabetes who experience frequent hypoglycemia or extreme glycemic lability. Patients who are well controlled with conventional insulin regimens would not be candidates for islet transplantation because of the lifelong need for immunosuppressant therapy.

Future directions for β-cell replacement include development of β-cells from stem cell lines, creating β-like cells (from non-β-cells), increasing β-cell replication (similar to the compensatory increase seen in obese and insulin-resistant patients), encapsulation of β-cells prior to transplantation for protection (against autoimmune attack), and xenotransplantation from porcine donors.

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