B. Gallwitz · U. R. Fölsch

Physiology and Pathophysiology of Endocrine Pancreatic Secretion

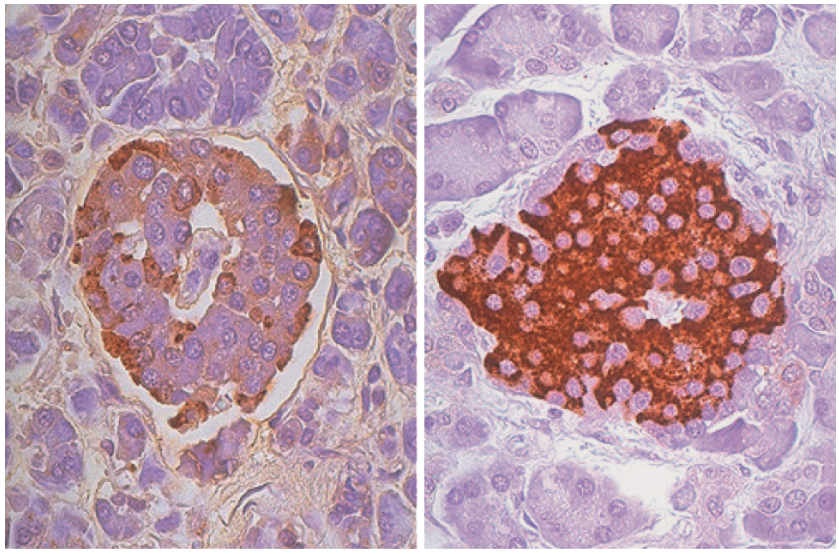
Approximately 2% of the human pancreas is comprised of the islets of Langerhans, which represent the vast majority of endocrine pancreatic tissue. In addition, small clusters of endocrine cells are dispersed within the exocrine tissue [1]. Four endocrine cell types have been identified in the islets (Fig. 5.1, Table 5.1): A-cells, which generate glucagon, B-cells, which produce insulin and islet amyloid polypeptide (IAPP, also referred to as amylin), D-cells, which synthesize somatostatin, and PP-cells, which produce pancreatic polypeptide (PP). A rapid exchange of substrates and hormones is guaranteed between the blood stream and the islets due to a higher perfusion of the islets in comparison to the exocrine pancreatic tissue and to an endothelial fenestration in the capillaries of the islets [2]. Capillaries first reach the B-cells, then the A-cells, and finally the D-cells, so that insulin may have a direct influence on the other islet cell types, whereas glucagon and somatostatin reach the B-cells via the general circulation [2]. Paracrine interaction between the different cell types, especially between D-Cells and the other endocrine cells, is also possible.

The islets of Langerhans are innervated by sympathetic and parasympathetic nerve fibers. The parasympathetic fibers originate from the vagus nerve and have their synapses in the intrapancreatic cholinergic ganglia. In addition to the classical sympathetic and parasympathetic neurotransmitters, peptidergic nerves containing vasoactive intestinal peptide (VIP), cholecystokinin (CCK), peptide histidine isoleucine (PHI), pituitary adenylate-cyclase-activating peptide (PACAP), and other neuropeptides are involved in regulating pancreatic endocrine and exocrine function. Vagal stimulation releases insulin and may play a role in the cephalic phase of insulin secretion, whereas stimulation of the sympathetic nerve fibers inhibits insulin secretion. Despite extensive research, it still remains largely unknown which physiological functions can exactly be assigned to the various types of innervation of the islets of Langerhans in man. Interestingly, the extrinsic denervation of the human pancreas, as occurs in pancreas transplantation, has only minor consequences on the endocrine function of the organ. Table 5.2 summarizes the pancreatic neuropeptides and their function in controlling pancreatic endocrine secretion [3].

Table 5.1. Endocrine cells in the islets of Langerhans and their secretory products (with permission [1]). *GRPP* Glucagon-related polypeptide, *IAPP* islet amyloid polypeptide

Cell type	Main secretion product	Secretory granules	Peptide length (number of amino acids)	Peptide size [molecular mass (Da)]	Overall abundance [%]	Minor products
A-cells	Glucagon	α	29	3,500	15–20	Major proglucagon fragment GRPP
B-cells	Insulin	β	51	5,800	70–80	C-peptide, proinsulin IAPP (amylin)
D-cells	Somatostatin 14	δ	14	1,500	5–10	–
PP-cells	Pancreatic polypeptide	–	36	1,200	15–25*	–

* Dorsal pancreas <1%; ventral pancreas 80%

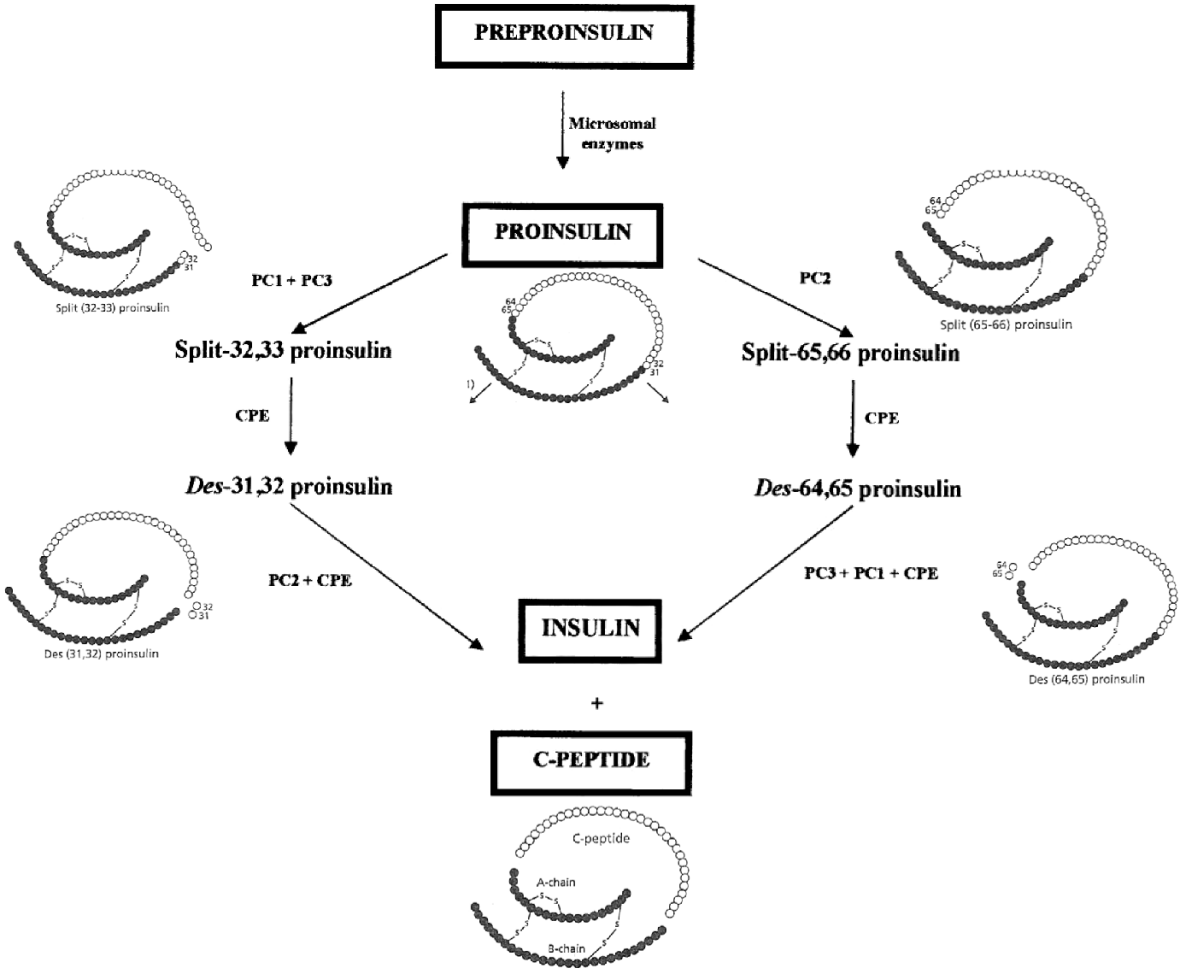


Figurge 5.1

Islets of Langerhans, microscope section. The islet is situated within the exocrine tissue (hematoxilin-eosin stain). The islet itself is presented with immunoperoxidase staining for glucagon on the left and insulin on the right. The A-cells on the left are stained brownish by peroxidase staining for glucagon; the right side of the figure shows the corresponding staining for insulin in the B-cells. Note the different distribution and number of cells, with A-cells being located at the periphery of the islet and B-cells being abundant in the center

Table 5.2. Pancreatic neuropeptides that might participate in the neural control of islet secretion (with permission, modified from [1]). *VIP* Vasoactive intestinal peptide, *PACAP* pituitary adenylate-cyclase-activating peptide, *PHI* peptide histidine isoleucine, *CCK* cholecystokinin, *GRP* gastrin-releasing peptide (mammalian bombesin), *CGRP* calcitonin gene-related peptide, *NPY* neuropeptide Y

	Pancreatic localization			Effect on		
Peptide	Nerves	Reaching islet cells	Control by	Insulin	Glucagon	Somatostatin
Stimulatory						
VIP	Yes (intrinsic ganglia)	Yes	Vagus	↑	↑	?
PACAP	Yes	Yes	?	↑	?	?
PHI	Yes	Yes	Vagus	↑	↑	?
Cholecystokinin (CCK 4, tetragastrin)	Yes (postganglionic fibers)	Yes	?	↑	↑	↑
GRP	Yes	?	Vagus	↑	-	↑
Substance P	Yes	?	?	↑	↑	↑
Inhibitory						
Galanin	Yes	Yes	Sympathetic nervous system	↑	↑	↑
CGRP	Yes	Yes	?	↑	-	↑
NPY	Yes	Yes	Sympathetic nervous system	↑	?	?



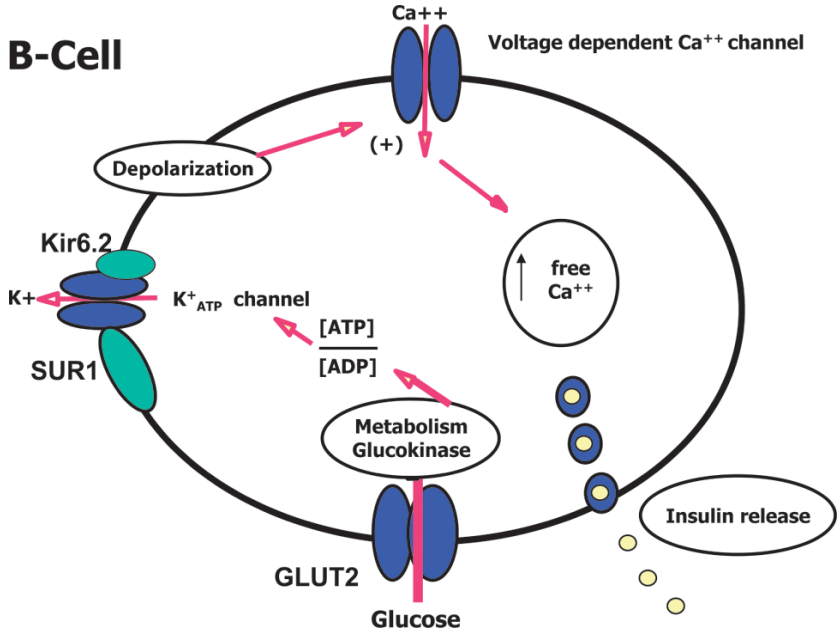
Figurge 5.2

Posttranslational processing of proinsulin (with permission, modified from [3]). Schematic diagram. Insulin is formed via conversion intermediates by the action of proprotein convertases (PC) 2 and 3 (*PC2* and *PC3*, respectively) and carboxypeptidase H (*CPE*)

The Cellular Physiology of Insulin Synthesis and Secretion

Insulin is the most important hormone of the endocrine pancreas since it is the major regulator of anabolic and metabolic processes. It is responsible for the uptake of glucose and amino acids into the peripheral tissues and for metabolic reactions leading to energy storage, such as glycogen synthesis. Generally, plasma glucose and amino acid concentrations are kept within a close range by insulin due to a very effective direction of these substrates into the respective target tissues (e.g., muscle, liver, adipose tissue) under varying metabolic situations and demands (e.g., after a meal, during physical activity). Diminished insulin secretion may lead to diabetes mellitus, whereas an inadequately high output of insulin from the B-cells causes hypoglycemia.

B-cells synthesize the larger insulin precursor molecule preproinsulin. Already in the endoplasmic reticulum, the signal sequence of the peptide is cleaved off and the resulting 86 amino acids containing proinsulin is stored in the Golgi vesicles. Proinsulin has a helical structure with two disulfide bridges connecting the C-terminal and N-terminal part of the peptide chain. In the Golgi vesicles, under acidic conditions and increased calcium concentrations, the enzymes proprotein convertase PC2 and proprotein convertase PC3 as well as carboxypeptidase H cleave the proinsulin chain along the positions 31–32 and



Figurge 5.3

Molecular mechanism of insulin secretion. Schematic diagram. Glucose enters the B-cell via the glucose transporter GLUT2. Intracellularly, glucose is metabolized, the first enzymatic step is phosphorylation by glucokinase. This leads to a shift in the ATP/ADP ratio and closing of the ATP-dependent K^+-channel. This channel is a hetero-octameric protein composed of the inwardly rectifying K^+ channel Kir6.2 and the sulfonylurea receptor SUR1 subunits. The B-cell consecutively depolarizes and the concentration of intracellular free Ca^{++} rises, finally leading to exocytosis of insulin granules

64–65 of the peptide chain, resulting in equimolar amounts of C-peptide and insulin. The posttranslational processing of proinsulin is shown in Fig. 5.2 [4]. Only around 5% of the proinsulin is not completely converted to C-peptide and insulin.

Mature insulin storage granules are formed independently of the actual need for insulin, so that the rate of insulin synthesis does not parallel the rate of insulin secretion, although nutrients play a role in the stimulation of both synthesis and secretion. Excess insulin is stored in the B-cells until it is released by an appropriate stimulatory signal for secretion [5].

The primary stimuli for insulin secretion are glucose and some amino acids, (predominantly arginine, lysine, leucine, and phenylalanine), which can initiate insulin secretion from B-cells at appropriate plasma concentrations [6]. Besides these primary stimuli, various modulators of insulin secretion interact with glucose-induced insulin secretion. The incretin hormones gastric inhibitory polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) are important physiological modulators of insulin secretion, which in the presence of normal fasting glucose concentrations have little effect on insulin secretion, but greatly stimulate insulin release under hyperglycemic conditions [7].

Glucose-induced insulin secretion is mediated by a B-cell-specific mechanism of glucose uptake and metabolism. Glucose is taken up into the B-cell very rapidly through the fast glucose transporter GLUT-2, which is specific for B-cells and hepatocytes. Intracellularly, glucose is then immediately phosphorylated by the B-cell-specific enzyme glucokinase, a reaction that is characterized by a high Michaelis constant (K_m) toward glucose. This enzyme works as intracellular "glucose sensor," since the glucose flux through glucokinase to form glucose-6-phosphate explains the quantitative relationship of extracellular glucose concentrations and the rate of glucose-induced insulin secretion [8]. Glucose-6-phosphate is then metabolized, finally generating adenosine triphosphate (ATP). A rise in ATP closes an ATP-dependent potassium (K^+) channel (KATP) present in the plasma membrane of the B-cell. This channel belongs to a family of KATP channels that are hetero-octameric proteins composed of an inwardly rectifying K^+ channel (Kir6.x) and sulfonylurea receptor (SUR) subunits. Different combinations of Kir6.x and SUR subunits comprise KATP channels with distinct electrophysiological and pharmacological properties. In the B-cell, the predominant type of KATP channel is the

Kir6.2 type, together with the SUR1 sulfonylurea receptor. The closure of this K^+ channel leads to a depolarization of the cell membrane with a consecutive activation of a voltage-dependent L-type calcium (Ca^{2+}) channel that promotes Ca^{2+} entry into the cytoplasm. A rise in cytoplasmic Ca^{2+} finally causes exocytosis of insulin-containing secretory granules [9]. The mechanism of glucose-induced insulin secretion is demonstrated in Fig. 5.3.

Amino acids may also serve as metabolic fuels to promote ATP synthesis, like glucose, and may therefore depolarize B-cells and lead to the stimulation of insulin secretion. Arginine as a highly charged cationic amino acid may directly depolarize B-cells upon transport into the cytoplasm.

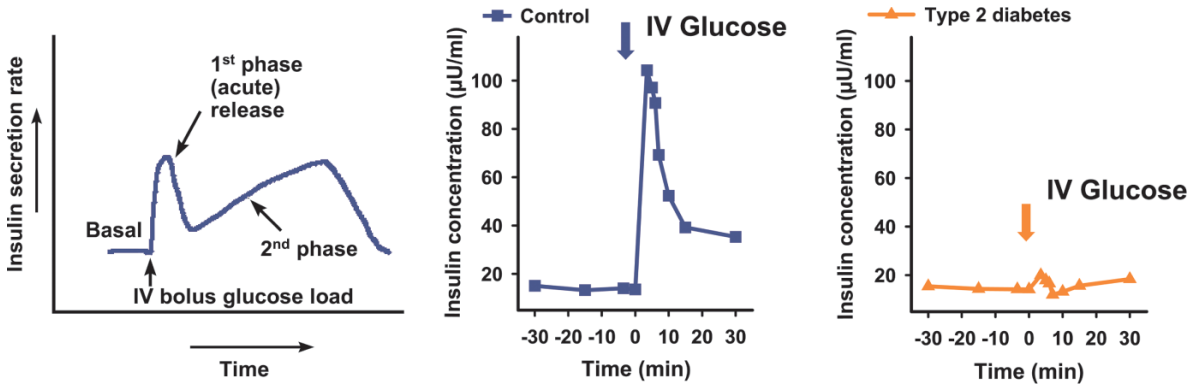
The incretin hormones GIP and GLP-1 stimulate cyclic AMP (cAMP) production via activation of the adenylate cyclase. This in turn leads to an increase in intracellular Ca^{2+} and also the phosphorylation of islet proteins, regulating the exocytosis of insulin granules [7].

Stimulation of Insulin Secretion in Man In Vivo

An intravenous infusion or injection of glucose with a rapid and large change in plasma glucose concentrations provokes a biphasic insulin secretory response in healthy subjects, with a quick, short, and pronounced first phase of insulin secretion within the first 20 min after glucose application and a slower and less pronounced second phase of insulin secretion (see Fig. 5.4). Changes in plasma glucose concentrations within physiological variations (between 80 and 150 mg/dl, corresponding to 4.4–8.3 mmol/l) release only minor amounts of insulin, indicating that there are additional stimuli for insulin secretion following a meal [10,11]. In healthy subjects, oral glucose induces dose-dependent insulin secretion with peak insulin concentrations occurring after 45–60 min postprandially (see Fig. 5.4). The stimulation of insulin secretion depends not only on B-cell characteristics, but also on other factors related to cephalic stimulation, such as taste, gastrointestinal motility such as gastric emptying, absorption of nutrients, systemic release of incretin hormones, and the sensitivity of B-cells towards the increments in glucose [3].

Insulin is not secreted steadily with continuous transitions from a low to a high secretion rate, but rather in a pulsatile manner. Pulses with different periodicity have been observed: rapid pulses, occurring at a periodicity of roughly 12–14 minutes, and slower pulses that occur approximately every 90 min. The rapid pulses originate in the islets themselves and are not initiated by extrinsic nerve stimulation, as the rapid pulses of insulin secretion are also observed in pancreatic transplants and even in transplanted islets. Pulsatile insulin secretion is biologically more effective at lowering plasma glucose than a continuous insulin secretion. Interestingly, this pulsatile insulin secretion is already lost or diminished in the very early stages of both types of diabetes mellitus, type 1 and type 2 [12].

Through a feedback-loop of insulin binding to insulin receptors on B-cells, insulin secretion is modi-

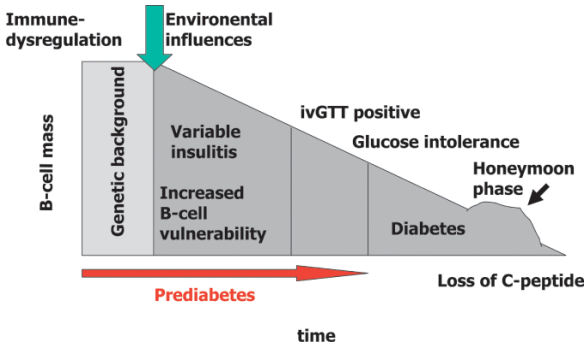


Figurge 5.4

First and second phase of insulin secretion after an intravenous (*IV*) glucose bolus (with permission, modified from [3]). On *top* is shown a schematic diagram of the first and second phase of insulin secretion. The diagram on the *left* shows the normal first phase of insulin secretion after an intravenous glucose bolus in normal subjects, the diagram on the *right* shows the loss of the first phase of insulin secretion in patients with type 2 diabetes

fied by its own release in an inhibitory manner. This feedback is operative only at basal glucose concentrations. Small rises in plasma glucose already disturb this feedback loop [3].

Gastrointestinal factors stimulate insulin secretion after a meal. Physiological studies have shown that orally administered glucose evokes a greater insulin response than an intravenously administered glucose infusion calculated to lead to exactly the same serum glucose excursions. This difference in the insulin response was named the "incretin effect," and the gastrointestinal hormones stimulating insulin secretion after oral glucose ingestion, mainly GIP and GLP-1, were called "incretins". The metabolic, neural, and hormonal effects of the small intestine on the endocrine pancreas are referred to as the "enteroinsular axis". Approximately 30–60% of the C-peptide response, and 80–90% of the insulin response after an oral glucose load are conveyed by incretin hormones in nondiabetic subjects, depending on the amount of glucose [7,11].



Figurge 5.5

Development of type 1 diabetes. The loss of B-cell function over time is shown along with pathological tests during that development. The environmental factors that trigger the autoimmune response leading to type 1 diabetes in genetically susceptible subjects have yet to be identified. Certain genetically determined constellations in the major histocompatibility complex (MHC-II) show a higher predisposition to type 1 diabetes and other autoimmune diseases. *ivGTT* Intravenous glucose tolerance test

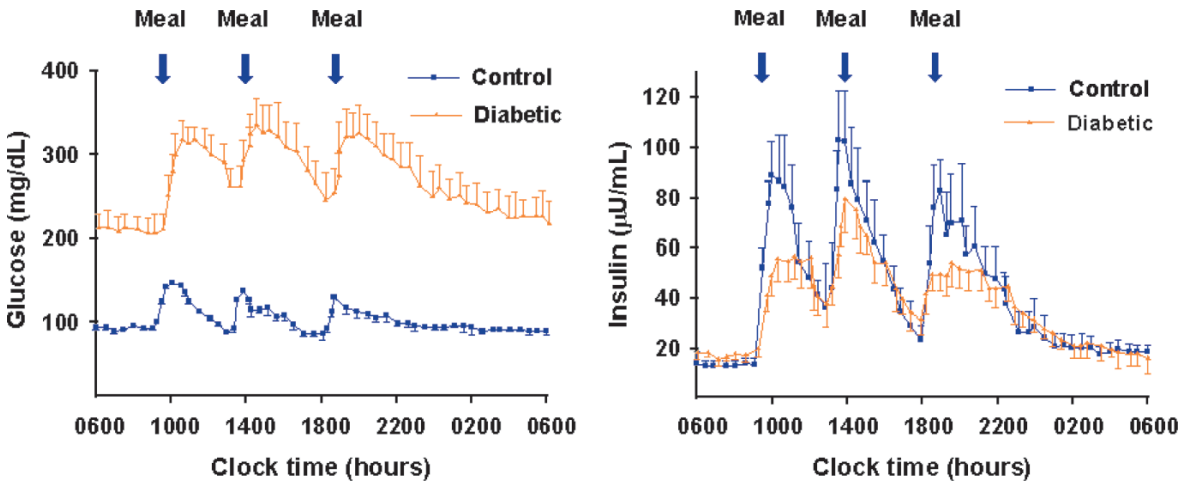
Pathophysiology of Insulin Secretion

Type 1 Diabetes Mellitus

Type 1 diabetes is an autoimmune disease that leads to the destruction of B-cells. T-lymphocytes infiltrate the islets and progressively destroy the B-cells over time. Insulin deficiency is so profound that ketoacidosis – the biochemical hallmark of type 1 diabetes – will develop unless insulin replacement is given. Nevertheless, even in longstanding type 1 diabetes, some insulin-positive B-cells can still be found. Disorders of insulin secretion can be related to the progressive loss of B-cells, with the occurrence of clinically overt diabetes when approximately 80–90% of B-cells are destroyed [13]. Typical autoantibodies of type 1 diabetes (islet cell antibodies, glutamate decarboxylase antibodies, insulin autoantibodies) are often present long before an impairment of insulin secretion can be detected. The first abnormality that can be detected under investigational conditions still in the state of normal oral glucose tolerance is the deterioration of the first phase of insulin secretion after an intravenous glucose injection. This defect is highly predictive of the development of type 1 diabetes within a short time. In clinically apparent type 1 diabetes, oral glucose tolerance declines and insulin and C-peptide plasma concentrations fall. Consecutively, fasting glucose concentrations become elevated, and finally, insulin deficiency is so pronounced that lipolysis is stimulated, leading to an accumulation of ketone bodies. After initial insulin treatment, a partial recovery of insulin secretion occurs in most patients for a transient period of a few months (called the "honeymoon phase"), which allows a drastic reduction of the initial insulin doses required. In longstanding type 1 diabetes, the C-peptide concentrations (a marker of residual B-cell function) are extremely low. Nevertheless, there is evidence that in a significant proportion of patients there is still a very small amount of remaining insulin secretion that is associated with better glycemic control. Early and sufficient insulin replacement may preserve residual B-cell function [14]. A schematic of the development of type 1 diabetes is shown in Fig. 5.5.

Type 2 Diabetes

Type 2 diabetes is on the one hand characterized by insulin resistance of the peripheral tissues, mainly the muscle, the liver, and adipose tissue, and on the other hand, impaired insulin secretion also plays an important role in the pathophysiology of this disease. Obese humans with the prediabetic condition of impaired fasting glucose (IFG) or type 2 diabetes, and lean subjects with type 2 diabetes already have a significant deficit of 40–60% in relative B-cell volume compared with nondiabetic obese and lean cases, respectively. This is due to an increase in B-cell apoptosis that is



Figurge 5.6

Twenty-four-hour profiles of glucose concentrations and insulin secretion profiles in healthy subjects and patients with type 2 diabetes (with permission, modified from [16]). Note the relative decrease in prandial insulin secretion in the diabetic patients. The glucose profiles are shown in the *left* panel, the insulin secretion plasma concentrations on the *right*

tenfold in lean and threefold in obese cases of type 2 diabetes compared with their respective nondiabetic controls. New islet formation and B-cell replication are normal. The frequency of B-cell apoptosis is related to the rate of increase of islet amyloid and IAPP oligomers, but islet amyloid is not responsible for increased B-cell apoptosis. Replicating B-cells are more vulnerable to apoptosis, possibly accounting for the failure of B-cell mass to expand appropriately in response to obesity in type 2 diabetes [15].

Glucose-induced insulin secretion in patients with type 2 diabetes is diminished and sluggish. The reason is a prominent loss of the first phase of insulin secretion after a sharp rise in glucose that occurs very early in the disease. The second phase of insulin secretion is also affected and gradually deteriorates with the progression of the disease [16]. In addition, the regularity of the pulsatile release of insulin is lost early in the disease and may already be absent in first-degree relatives of patients with type 2 diabetes with normal glucose tolerance. Other stimuli of insulin secretion also show a diminished effect of varying degrees [3]. Of the incretin hormones, GLP-1 still exerts a stimulatory effect on insulin secretion under hyperglycemic conditions in pharmacological doses, making GLP-1-based "incretin mimetics" or dipeptidyl-peptidase IV (DPP IV) inhibitors preventing the degradation of endogenous GLP-1 a promising new treatment option for type 2 diabetes [7,17].

The fact that with improvement of metabolic control, type 2 diabetic B-cells partially recover, has pointed to some direct and partially reversible effects of hyperglycemia itself on B-cell function. This phenomenon, together with the influence that hyperglycemia exerts on insulin sensitivity, has been termed glucose toxicity. Also, free fatty acids, which are characteristically elevated in patients with type 2 diabetes, impair insulin secretion [18]. Figure 5.6 shows the characteristic diurnal profiles of glucose concentrations and insulin secretion rates in patients with type 2 diabetes [16].

Other Types of Diabetes in Pancreatic Disease

Maturity-onset diabetes of the young (MODY) is a genetically and clinically heterogeneous subtype of familial diabetes mellitus that is characterized by early onset, autosomal dominant inheritance and primary defects of insulin secretion. Mutations in six genes are the cause most of the MODY cases. These genes encode the enzyme glucokinase and the transcription factors hepatocyte nuclear factor 4α, hepatocyte nuclear factor 1α, insulin promoter factor-1, hepatocyte nuclear factor 1β, and neuro D1. Additional MODY genes remain to be identified. The study of families with MODY has shown that the different MODY subtypes present different metabolic and clinical profiles, most of them with a defect in insulin secretion due to a reduced activity of glucokinase and consecutive shift to the right in the glucose concentration–insulin secre-

tory response curve. Insulin secretion to an arginine stimulus is not affected in most types of MODY [19].

Chronic pancreatitis with exocrine insufficiency is accompanied by diabetes in approximately 10% of all cases, with 30% of the patients showing an impaired glucose tolerance. The underlying cause is the increasing fibrosis of the pancreas in chronic pancreatitis and the concomitant loss of B-cells. The deterioration of endocrine function is correlated with the loss of exocrine function. There may be an accentuated loss of B-cells relative to A-cells, but clinically counter-regulation in hypoglycemia by glucagon is often impaired in patients with chronic pancreatitis [3].

Physiology of Glucagon Secretion

Glucagon is a peptide that contains 29 amino acids and is secreted by the A-cells. The main function of glucagon in humans is to modulate hepatic glucose output, which needs to be maintained during fasting states and increased energy demands (e.g., exercise). After glucagon binding to a specific G-protein-coupled receptor on the hepatocyte membrane, cAMP is generated and protein phosphorylation via protein kinase A is stimulated. Via this activation cascade, the enzymes involved in glycogenolysis and gluconeogenesis provide glucose for the organism. Hepatic ketogenesis producing β-hydroxybutyrate and acetoacetate from free fatty acids via acetyl coenzyme A is also promoted by glucagon [3].

Hypoglycemia promotes glucagon release, whereas in healthy subjects, hyperglycemia is inhibitory. Oral carbohydrate intake therefore suppresses glucagon secretion. In parallel with the aforementioned incretin effect, the suppression of glucagon secretion is more pronounced when glucose or carbohydrates are ingested by comparison to an intravenous glucose infusion. Amino acids stimulate glucagon release and are responsible for the rise in plasma glucagon concentrations after a mixed meal containing proteins. Activation of the adrenergic system by exercise, stress, or fever also leads to an increase in glucagon secretion [3,20].

Pathophysiology of Glucagon Secretion

Type 1 Diabetes

Insulin deficiency promotes hyperglucagonemia in type 1 diabetes. Since a major determinant of glucagon action is the plasma concentration of glucose in the portal blood relative to that of insulin, type 1 diabetes is characterized by a low insulin to glucagon ratio, leading to a propensity for increased hepatic glucose output. Elevated glucagon levels may also contribute to the increased lipolysis observed in type 1 diabetes and can therefore contribute to ketone-body formation and thus to the risk of developing ketoacidosis [3].

Glucagon is, along with the catecholamines, a very important hormone in first-line endocrine counter-regulation in hypoglycemia. Repeated and frequent hypoglycemia leads to a blunting of the counter-regulatory response of glucagon secretion that can only be overcome by meticulous avoidance of frequent hypoglycemia. Furthermore, with the progression of type 1 diabetes and long-term changes in islet architecture, A-cells additionally become increasingly insensitive to changes in the plasma glucose concentrations and a further defect in glucagon secretion under hypoglycemic conditions is observed [3,21].

Type 2 Diabetes

In type 2 diabetes, a relative excess of circulating glucagon is observed. Hyperglycemia does not adequately suppress glucagon release, so that plasma glucagon concentrations are normal or elevated instead of decreased. The reasons for this phenomenon are not completely clear, possible explanations could be an intrinsic defect in glucose recognition by A-cells, insulin resistance of the A-cells themselves or desensitization of the A-cells due to chronic hyperglycemia. Glucagon excess will contribute to increased hepatic glucose production and an impaired ability to suppress hepatic glucose output by insulin, resulting in a perpetuation of hyperglycemia. The incretin hormone GLP-1 is able to suppress glucagon secretion in type 2 diabetes effectively [3].

Somatostatin and Pancreatic D-cells

Somatostatin is a peptide hormone and neurotransmitter that is found ubiquitously in the hypothalamus, in the endocrine cells of the mucosa of the stomach and small intestine, and in the D-cells of the pancreas. It was first isolated from the hypothalamus, where it inhibits pituitary growth hormone secretion. There are two molecular forms, somatostatin 14, which has 14 amino acids, and the longer somatostatin 28, which are formed by alternative processing. In the D-cell, somatostatin 14 is the predominant form [22].

D-cells have long cytoplasmic processes in contact with other islets cells and capillaries, which facilitate their paracrine activities. Pancreatic somatostatin primarily inhibits insulin and glucagon secretion. The glucagon suppression in hyperglycemia is thought to be mediated by somatostatin [3].

Somatostatin from D-cells is secreted in response to elevated plasma glucose and glucagon concentrations and by insulin deficiency. In insulin deficiency, the stimulation of somatostatin release might be mediated indirectly by hyperglycemia, free fatty acids, and ketone bodies. Amino acids, peptide hormones, and various neurotransmitters (see Table 5.2) are additional secretagogues. Pancreatic somatostatin has profound effects on the secretion of other islet hormones, but it contributes only little to the circulating levels of somatostatin, which is mostly the somatostatin 28 secreted by the gut [3].

Pancreatic Polypeptide

PP is a peptide that contains 36 amino acids and is secreted by the PP-cells. Islets with a larger proportion of PP-cells are located mainly in the dorsal part of the head of the pancreas; islets in other locations of the pancreas contain only a few PP-cells. Protein and fat in meals are secretagogues for the release of PP via vagal cholinergic pathways. PP may physiologically inhibit pancreatic exocrine function and gallbladder contraction, opposing the effect of CCK, or it may have trophic effects on the pancreas. PP also has anorectic properties and has been shown to terminate feeding in animals [3]. PP does not have any stimulatory or inhibitory effect on other islet hormones.

Islet Amyloid Polypeptide (IAPP, Amylin)

Amylin, which was first discovered in 1987, is cosecreted with insulin from the B-cells. Pancreatic amylin acts as a short-term satiety hormone mainly by binding to specific binding sites in the hypothalamus. It is released during meals; exogenous amylin leads to a dose-related reduction in meal size. Amylin's anorectic effect may in part be due to reduced expression of orexigenic neuropeptides in the lateral hypothalamic area. The anorectic action of amylin is one important factor in amylin's overall role to control the influx of nutrients into the circulation. By reducing food intake and gastric acid secretion, limiting the rate of gastric emptying, and diminishing pancreatic glucagon and digestive enzyme secretion, amylin regulates nutrient disappearance and postprandial glucose concentration. Amylin seems to be a necessary and complementary factor to insulin, which regulates the rate of nutrient disappearance. In this sense, amylin and insulin are adjunct players in the control of nutrient fluxes, and amylin's role to control feeding is a pivotal factor in this regard [23].

Amylin is thus deficient in diabetic people. Amylin replacement could therefore possibly improve glycemic control in some people with diabetes. However, human amylin exhibits physicochemical properties that predispose the peptide hormone to aggregate and form amyloid fibers, which may play a part in B-cell destruction in type 2 diabetes. This obviously makes it unsuitable for pharmacological use. A stable analog, pramlintide (Symlin), which has actions and pharmacokinetic and pharmacodynamic properties similar to the native peptide, has been developed and recently approved as an adjunct therapeutic agent for patients with type 1 or type 2 diabetes treated with insulin and not achieving the desired metabolic control [24].

Pancreas and Islet Transplantation

Since 1921 and until recently, insulin by injection has been the only treatment for patients with diabetes mellitus type 1. Pancreas transplantation is currently the curative treatment for type 1 diabetes mellitus. It aims at providing physiological insulin replacement therapy for type 1 diabetes mellitus. The goal is thereby also to prevent the secondary complications of diabetes. Long-term control of glucose metabolism has only been achieved by pancreas transplantation. As a result of improvements in the surgical techniques and the efficacy of immunosuppression, the patient and graft survival rates have improved dramatically over the last two decades. As a result, pancreas transplantation, as part of simultaneous pancreas and kidney transplantation, pancreas after kidney transplantation, and exceptionally pancreas transplantation alone, has become the standard therapeutic option for patients with type 1 diabetes mellitus with end-stage renal disease [25].

After pancreas transplantation, which became possible in 1977, the next logical step to cure patients with diabetes mellitus type 1 is transplantation of the islets of Langerhans. In the last few years, the results of islet transplantation have markedly improved thanks to progress in the isolation technique of islets and better immunosuppressive protocols. In addition, the islets are infused into the portal circulation, where

Table 5.3. Enteroendocrine tumor syndromes other than carcinoid (with permission, modified from [27]). *SSTA* somatostatin analog, *WDHA* watery diarrhea-hypokalemia-achlorhydria, *ACTH* adrenocorticotropic hormone, *PTHrP* parathyroid-hormone-related peptide, *GRH* growth-hormone-releasing factor

Tumor	Syndrome	Hormone	Clinical features	Site	Percent malignant	Treatment
Insulinoma	Insulinoma	Insulin proinsulin	Hypoglycemia Weight gain	>95% Pancreas	>10	Surgery, diet intravenous dextrose, chemotherapy, diazoxide, SSTA
Gastrinoma	ZES	Gastrin	Abdominal pain, peptic ulceration, diarrhea, gastric hypersecretion	Duodenum 70%, pancreas 25%	60–90	Proton pump inhibit, surgery, SSTA, chemotherapy
VIPoma	Verner-Morrison pancreatic cholera WDHA	VIP	Secretory diarrhea hypokalemia, achlorhydria, metabolic acidosis, flushing, weight loss	90% Pancreas	>50	Intravenous fluids, surgery, SSTA, chemotherapy
Glucagonoma	Glucagonoma syndrome	Glucagon	Diabetes, necrolytic migratory erythema, deep vein thrombosis, depression	Pancreas	>50	Surgery, diet, SSTA, insulin, anticoagulant, chemotherapy
Somatostatinoma	Somatostatinoma syndrome	Somatostatin	Diabetes, gallstones, weight loss, steatorrhea	Pancreas 56%, upper intestine 44%	70–80	Surgery, insulin, pancreatic enzymes
Extremely rare tumors						
ACTHoma	Ectopic Cushing's syndrome	ACTH	Hypertension, diabetes, weakness	Pancreas 30%, lung 50%	>99	Surgery, chemotherapy, SSTA
PTHrPoma	Hyperparathyroidism	Parathyroid hormone-related peptide	Hypercalcemia, nephrolithiasis	Pancreas	>99	Surgery, chemotherapy
Neurotensinoma	?	Neurotensin	Diabetes, diarrhea, flushing, hypertension, weight loss, edema	Pancreas	?	Surgery, chemotherapy
Calcitoninoma	?	Calcitonin	?	Pancreas, lung	>80	Surgery, chemotherapy
GRFoma	Acromegaly	Growth hormone-releasing factor	Acromegaly	Pancreas, lung, thymus	30	Surgery, SSTA

they can function more physiologically than in the peripheral circulation, as in whole organ pancreatic transplants. More than 470 patients with type 1 diabetes have received islet transplants at 43 institutions worldwide in the past 5 years. High rates of insulin independence have been observed at 1 year in the leading islet transplant centers, and an international multicenter trial has demonstrated reproducible success of the approach. Loss of insulin independence by 5 years in the majority of recipients remains of concern. Ongoing problems in islet transplantation are alloimmunity, autoimmunity, and the growing shortage of donor pancreases. Alternatives to pancreas donation, be it post mortem or from a living donor, could be: xenotransplantation with the aid of pig islets, and B-cell neogenesis from embryonic stem cells or pancreatic duct cells [26].

Insulinomas and Other Endocrine Tumors of the Pancreas

Clinically significant pancreatic endocrine tumors (PET) have been reported to occur in approximately 1 per 100,000 people per year and account for only 1–2% of all pancreatic tumors. Insulinomas are the most common functioning PETs, with a 17% incidence, followed by gastrinoma (15%), PPoma (9%), VIPoma (2%), glucagonoma (1%), carcinoid (<1%), and somatostatinoma (1%); the remainder are comprised of neurotensinomas, adrenocorticotropic hormeoma (ACTHoma), GRFomas, calcitonin-producing tumors, parathyroid-hormone-related peptide tumors, and other exceedingly rare neoplasms. This whole group of very rare PETs accounts for no more than 1–2% of the group of all PETs. It must also be borne in mind that almost all of the PETs can be multiple and can arise outside of the pancreas, particularly gastrinomas (<77%), carcinoids (99%), and somatostatinomas (>40%). Nonfunctioning PETs comprise the largest group of these tumors (15–30%). Table 5.3 gives an overview on the clinical features of the most abundant PETs.

Neuroglycopenic symptoms with repeated episodes of hypoglycemia are present in almost all insulinoma patients. The symptoms are transiently relieved by the administration of carbohydrates. These symptoms are called Whipple's triad. Inappropriately high and autonomous secretion of insulin and proinsulin at rates that are not determined by metabolic needs are the cause for the recurrent hypoglycemias. Cardiovascular symptoms are the main presenting features in 17%. The most common clinical test used when a patient is suspected to have an insulinoma is prolonged fasting (for at least 48 h if hypoglycemia does not develop within shorter periods) with frequent blood sampling for the measurement of glucose, insulin, C-peptide, and if possible proinsulin. Diagnostic accuracy may be improved by using an "amended" insulin to glucose ratio with a normal value of <0.5 (mU/ml)/(mg/dl). This ratio is obtained by subtracting 30 mg/dl from the plasma glucose value, so that the glucose value may become zero or negative (with ∞ values for the ratio) when the plasma glucose falls below 30 mg/dl. Almost all insulinomas (97%) are located in the pancreas and most are small. One-half or more are undetected before surgery, but more than 90% can be localized by palpation alone or aided by intraoperative ultrasound. Surgery is the principal treatment for insulinomas. It has been noted that octreotide treatment may make hypoglycemia worse in insulinoma patients lacking the somatostatin receptor subtypes 2 (SSTr2) and 5 (SSTr5), and can therefore fail to suppress insulin production and may blunt the compensatory glucagon response. Hence, this treatment should be reserved for only the minority of insulinoma patients with positive imaging on somatostatin receptor scintigraphy (SRS) [3,27].

References

1. Klöppel G, Gepts W, In't Veld PA (1992) Morphology of the pancreas in normal and diabetic states. In: Alberti KGGM, DeFronzo RA, Kenn H, Zimmet P (eds) International Textbook of Diabetes Mellitus. John Wiley and Sons, Chichester, pp 223–259
2. Bonner-Weir S, Orci L (1982) New perspectives on the microvasculature of the islets of Langerhans in the rat. Diabetes 31:883–889
3. Nauck MA (1998) Physiology and pathophysiology of endocrine pancreatic secretion. In: Beger HG, Warshaw AL, Büchler MW, et al (eds) The Pancreas. Blackwell Science, Oxford, pp 101–137
4. Madsbad S, Hartling SG, Faber OK (1992) C-peptide and proinsulin. In: Alberti KGGM, DeFronzo RA, Kenn H, Zimmet P (eds) International Textbook of Diabetes. John Wiley and Sons, Chichester, pp 303–332
5. Hutton JC (1994) Insulin secretory granule biogenesis and the proinsulin-processing endopeptidases. Diabetologia 37 Suppl 2:S48–56
6. Malaisse WJ (1992) Insulin biosynthesis and secretion in vitro. In: Alberti KGGM, DeFronzo RA, Kenn H, Zimmet P (eds) International Textbook of Diabetes. John Wiley and Sons, Chichester, pp 261–283
7. Meier JJ, Nauck MA (2005) Glucagon-like peptide 1 (GLP-1) in biology and pathology. Diabetes Metab Res Rev 21:91–117
8. Matschinsky FM (1996) Banting Lecture 1995. A lesson in metabolic regulation inspired by the glucokinase glucose sensor paradigm. Diabetes 45:223–241

9. Minami K, Miki T, Kadowaki T, Seino S (2004) Roles of ATP-sensitive K+ channels as metabolic sensors: studies of Kir6.x null mice. Diabetes 53 Suppl 3:S176–180
10. Shapiro ET, Tillil H, Rubenstein AH, Polonsky KS (1988) Peripheral insulin parallels changes in insulin secretion more closely than C-peptide after bolus intravenous glucose administration. J Clin Endocrinol Metab 67:1094–1099
11. Creutzfeldt W (1979) The incretin concept today. Diabetologia 16:75–85
12. Porksen N, Hollingdal M, Juhl C, Butler P, Veldhuis JD, Schmitz O (2002) Pulsatile insulin secretion: detection, regulation, and role in diabetes. Diabetes 51 Suppl 1:S245–254
13. Bottazzo GF, Florin-Christensen A, Doniach D (1974) Islet-cell antibodies in diabetes mellitus with autoimmune polyendocrine deficiencies. Lancet 2:1279–1283
14. The DCCT Research Group (1987) Effects of age, duration and treatment of insulin-dependent diabetes mellitus on residual beta-cell function: observations during eligibility testing for the Diabetes Control and Complications Trial (DCCT). J Clin Endocrinol Metab 65:30–36
15. Butler AE, Janson J, Bonner-Weir S, Ritzel R, Rizza RA, Butler PC (2003) Beta-cell deficit and increased beta-cell apoptosis in humans with type 2 diabetes. Diabetes 52:102–110
16. Polonsky KS, Given BD, Hirsch LJ, et al (1988) Abnormal patterns of insulin secretion in non-insulin-dependent diabetes mellitus. N Engl J Med 318:1231–1239
17. Meier JJ, Gallwitz B, Nauck MA (2003) Glucagon-like peptide 1 and gastric inhibitory polypeptide: potential applications in type 2 diabetes mellitus. BioDrugs 17:93–102
18. Reaven GM, Hollenbeck C, Jeng CY, Wu MS, Chen YD (1988) Measurement of plasma glucose, free fatty acid, lactate, and insulin for 24 h in patients with NIDDM. Diabetes 37:1020–1024
19. Velho G, Robert JJ (2002) Maturity-onset diabetes of the young (MODY): genetic and clinical characteristics. Horm Res 57 Suppl 1:29–33
20. Jiang G, Zhang BB (2003) Glucagon and regulation of glucose metabolism. Am J Physiol Endocrinol Metab 284:E671–678
21. Mitrakou A, Ryan C, Veneman T, et al (1991) Hierarchy of glycemic thresholds for counterregulatory hormone secretion, symptoms, and cerebral dysfunction. Am J Physiol 260: E67–74
22. Reichlin S (1983) Somatostatin (parts 1 and 2). New Engl J Med 309:1495–1501; 1556–1563
23. Lutz TA (2005) Pancreatic amylin as a centrally acting satiating hormone. Curr Drug Targets 6:181–189
24. Schmitz O, Brock B, Rungby J (2004) Amylin agonists: a novel approach in the treatment of diabetes. Diabetes 53 Suppl 3:S233–238
25. Al-Shurafa HA, Jawdat MT, Bassas AF, Rogiers XC, Bechstein WO (2002) Innovations in pancreas transplantation. Saudi Med J 23:265–271
26. Shapiro AM, Lakey JR, Paty BW, Senior PA, Bigam DL, Ryan EA (2005) Strategic opportunities in clinical islet transplantation. Transplantation 79:1304–1307
27. Warner RR (2005) Enteroendocrine tumors other than carcinoid: a review of clinically significant advances. Gastroenterology 128:1668–1684