Pancreatic regulation of glucose homeostasis

Pia V Röder1, Bingbing Wu2, Yixian Liu2 and Weiping Han1,2

In order to ensure normal body function, the human body is dependent on a tight control of its blood glucose levels. This is accomplished by a highly sophisticated network of various hormones and neuropeptides released mainly from the brain, pancreas, liver, intestine as well as adipose and muscle tissue. Within this network, the pancreas represents a key player by secreting the blood sugar-lowering hormone insulin and its opponent glucagon. However, disturbances in the interplay of the hormones and peptides involved may lead to metabolic disorders such as type 2 diabetes mellitus (T2DM) whose prevalence, comorbidities and medical costs take on a dramatic scale. Therefore, it is of utmost importance to uncover and understand the mechanisms underlying the various interactions to improve existing anti-diabetic therapies and drugs on the one hand and to develop new therapeutic approaches on the other. This review summarizes the interplay of the pancreas with various other organs and tissues that maintain glucose homeostasis. Furthermore, anti-diabetic drugs and their impact on signaling pathways underlying the network will be discussed.

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THE PANCREAS IS AN EXOCRINE AND ENDOCRINE ORGAN

The pancreas has key roles in the regulation of macronutrient digestion and hence metabolism/energy homeostasis by releasing various digestive enzymes and pancreatic hormones. It is located behind the stomach within the left upper abdominal cavity and is partitioned into head, body and tail. The majority of this secretory organ consists of acinar—or exocrine—cells that secrete the pancreatic juice containing digestive enzymes, such as amylase, pancreatic lipase and trypsinogen, into the ducts, that is, the main pancreatic and the accessory pancreatic duct. In contrast, pancreatic hormones are released in an endocrine manner, that is, direct secretion into the blood stream. The endocrine cells are clustered together, thereby forming the so-called islets of Langerhans, which are small, island-like structures within the exocrine pancreatic tissue that account for only 1–2% of the entire organ (Figure 1). There are five different cell types releasing various hormones from the endocrine system: glucagon-producing α-cells, which represent 15–20% of the total islet cells; amylin-, C-peptide- and insulin-producing β-cells, which account for 65–80% of the total cells; pancreatic polypeptide (PP)-producing γ-cells, which comprise 3–5% of the total islet cells; somatostatin-producing δ-cells, which constitute 3–10% of the total cells; and ghrelin-producing ε-cells, which comprise <1% of the total islet cells. Each of the hormones has distinct functions. Glucagon increases blood glucose levels, whereas insulin decreases them. Somatostatin inhibits both, glucagon and insulin release, whereas PP regulates the exocrine and endocrine secretion activity of the pancreas. Altogether, these hormones regulate glucose homeostasis in vertebrates, as described in more detail below. Although the islets have a similar cellular composition among different species, that is, human, rat and mouse, their cytoarchitecture differs greatly. Although islets in rodents are primarily composed of β-cells located in the center with other cell types in the periphery, human islets exhibit interconnected α- and β-cells.

Through its various hormones, particularly glucagon and insulin, the pancreas maintains blood glucose levels within a very narrow range of 4–6 mM. This preservation is accomplished by the opposing and balanced actions of glucagon and insulin, referred to as glucose homeostasis. During sleep or in between meals, when blood glucose levels are low, glucagon is released from α-cells to promote hepatic glycogenolysis. In addition, glucagon drives hepatic and renal gluconeogenesis to increase endogenous blood glucose levels during prolonged fasting. In contrast, insulin secretion from β-cells is stimulated by elevated exogenous glucose levels, such as those occurring after a meal. After docking to its receptor on muscle and adipose tissue, insulin enables the insulin-dependent uptake of carbohydrates into cells.
glucose into these tissues and hence lowers blood glucose levels by removing the exogenous glucose from the blood stream (Figure 2). Furthermore, insulin promotes glycogenesis and lipogenesis and the incorporation of amino acids into proteins; thus, it is an anabolic hormone, in contrast to the catabolic activity of glucagon.

**THE INSULIN SECRETION SIGNALING PATHWAY**

Endocrine cells secrete their respective hormones in response to external signals, such as nutrient intake or stress, via humoral, neural or hormonal signaling pathways. The underlying molecular process that translates the stimulus into the actual hormone release is called stimulus-secretion coupling which is known as the stimulus-dependent exocytosis of a particular substance, such as glucose-stimulated β-cell insulin release.

In β-cells, the main stimulus for insulin release are elevated blood glucose levels following a meal. The circulating blood glucose is taken up by the facilitative glucose transporter GLUT2 (SLC2A2), which is located on the surface of the β-cells. Once inside the cell, glucose undergoes glycolysis, thereby generating adenosine triphosphate (ATP), resulting in an increased ATP/ADP ratio. This altered ratio then leads to the closure of ATP-sensitive K⁺-channels (K<sub>ATP</sub>-channels). Under non-stimulated conditions, these channels are open to ensure the maintenance of the resting potential by transporting positively charged K⁺-ions down their concentration gradient out of the cell. Upon closure, the subsequent decrease in the magnitude of the outwardly directed K⁺-current elicits the depolarization of the membrane, followed by the opening of voltage-dependent Ca⁺-channels (VDCCs). The increase in intracellular calcium concentrations eventually triggers the fusion of insulin-containing granules with the membrane and the subsequent release of their content. The whole secretory process is biphasic with the first phase peaking around 5 minutes after the glucose stimulus with the majority of insulin being released during this first phase. In the second, somewhat slower, phase, the remaining insulin is secreted. Insulin is stored in large dense-core vesicles that are recruited to the proximity of the plasma membrane following stimulation such that insulin is readily available. The key molecules that mediate the fusion of the insulin-containing large dense-core vesicles are the synaptosomal-associated protein of 25 kDa (SNAP-25), syntaxin-1 and synaptobrevin 2 (or vesicle-associated membrane protein VAMP2), all of which belong to the superfamily of the soluble N-ethylmaleimide-sensitive factor attachment protein (SNAP) receptor proteins (SNAREs). Together with the Sec1/Munc18-like (SM) proteins they form the so-called SNARE complex. To initiate fusion, synaptobrevin 2, a vesicle (v-)SNARE that is integrated into the vesicle’s membrane, fuses with the target (t-)SNAREs syntaxin-1 and SNAP-25, which are located in the target cell membrane, with mammalian uncoordinated (munc)-18 playing a key regulatory role (Figure 3).

To date, numerous SNARE isoforms, including syntaxin-1, -3 and -4, SNAP-25 and -23, as well as synaptobrevins 2 and 3 (VAMP2 and 3), have been shown to be involved in glucose-stimulated insulin secretion, whereas VAMP8, a non-essential SNARE protein for glucose-stimulated insulin secretion, has a role in the regulation of the glucagon-like
peptide-1-potentiated insulin secretion. In addition to SNARE and SM proteins, a calcium sensor is required for the initiation of membrane fusion. Synaptotagmins, which are highly expressed in neurons and endocrine cells, were shown to participate in Ca\(^{2+}\)-dependent exocytosis processes. To date, 17 synaptotagmins (Syts 1–17) have been identified and only eight of them, namely Syt-1, -2, -3, -5, -6, -7, -9 and -10, are able to bind calcium. Following Ca\(^{2+}\)-binding,
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synaptotagmins form a complex with the SNAREs to facilitate and trigger the vesicle-membrane fusion process. Among the synaptotagmin family, Syt-3, -5, -7, -8 and -9 are implicated in insulin exocytosis.49–52

EXTERNAL FACTORS AFFECTING PANCREATIC HORMONE SECRETION

Metabolism–cAMP coupling

The glucose-triggered stimulus-secretion coupling is an established paradigm of insulin secretion from β-cells and includes a great variety of modulators that trigger, potentiate or inhibit glucose-stimulated insulin secretion, primarily through G-protein-coupled receptors (GPCRs). The most traditional external factor that initiates insulin secretion is glucose. In addition to its trigger function, glucose also induces pathways that amplify insulin secretion through metabolism–cAMP (cyclic adenosine monophosphate) coupling or the incretin hormones glucagon-like peptide (GLP)-1 and glucose-dependent insulino-tropic peptide (GIP).31 Metabolism–cAMP coupling refers to the signaling cascade that occurs after the conversion of ATP, which is generated during intracellular glucose metabolism, into cAMP by adenylate cyclase (AC),53 which in turn activates protein kinase A (PKA)54 and cAMP-regulated guanine nucleotide exchange factors, also referred to as exchange protein directly activated by cAMP (Epac)55,56. Although Epac2 activation amplifies insulin secretion by mobilizing calcium from internal stores to increase Ca2+ levels57,58 and by controlling the granule density in proximity to the plasma membrane,59 activated PKA exerts its effects by modulating KATP-channel60,61 and calcium channel62,63 activity through phosphorylation, thereby enhancing the number of highly Ca2+-sensitive insulin-containing granules64 and the probability of releasing secretory vesicles from the readily releasable pool,65 respectively.

The incretins GLP-1 and GIP

The gut-derived hormones GLP-1 and GIP, which are secreted from enteroendocrine L-cells66 and K-cells,67 respectively, upon glucose,66,68 fructose,69 amino acid70 and free fatty acid (FFA)71,72 ingestion, also potentiate insulin release through the so-called incretin effect. This effect describes the observation that orally, but not intravenously, administered glucose enhances insulin secretion by triggering GLP-1 and GIP secretion;73–75 the resulting potentiation of insulin secretion may account for up to 50% of the total release. The underlying mechanism includes GLP-1 and GIP binding to their GPCRs (GLP-1R and GIPR), both of which are expressed in pancreatic β-cells.76 The binding induces a conformational change in the receptors’ structure, followed by the exchange of guanosine diphosphate for guanosine triphosphate and the subsequent dissociation of the Gα-subunit from the receptors. This subunit, in turn, activates adenylate cyclase to convert ATP into cAMP, thereby stimulating the cAMP signaling pathway described above.77–82 Furthermore, GLP-1 increases intracellular calcium concentrations by mobilizing Ca2+ from ryanodine-sensitive stores83,84 or, similar to GIP, by acting on voltage-dependent Ca2+-channels,85 thereby potentiating insulin release.85–87 Recent studies have also shown that GLP-1R agonists, such as exendin-488, induce the PKA-mediated phosphorylation of Snapin or Synaptotagmin-7, which in turn enhances GSIS by Snapin interacting with SNAP-2589 or by directly enhancing glucose- and Ca2+-triggered insulin release.90

Free Fatty Acids

FFAs not only stimulate incretin secretion but are also known to modulate insulin release through fatty acid metabolism. Although long-chain FFAs augment insulin secretion, short-chain FFAs inhibit it. The binding and subsequent interaction of long-chain FFAs with the G-protein-coupled free fatty acid receptor (FFAR) 1 in the pancreatic β-cells leads to the activation of phospholipase C. PLC then hydrolyzes phosphatidylinositol-4,5-bisphosphate (PIP2) to diacylglycerol and inositol-1,4,5-triphosphate (IP3), with the latter docking on a calcium channel in the endoplasmic reticulum. The subsequent release of Ca2+ into the cytosol increases the intracellular Ca2+ concentration, which eventually triggers insulin secretion.91–94 In contrast, short-chain FFAs inhibit glucose-stimulated insulin secretion due to decreased glucose oxidation and the subsequently decreased ATP/ADP ratio.95 Another inhibitor of insulin release is stress, specifically norepinephrine (noradrenaline) produced in response to stress.96 Norepinephrine binds to its α2-adrenergic receptors, which are linked to GPCRs, resulting in the inhibition of AC as well as in hyperpolarization. This prevents an increase in the cytosolic Ca2+ concentration and, subsequently, insulin secretion.97,98

INTERPLAY BETWEEN THE PANCREATIC ISLETS AND OTHER ORGANS

The brain–islet axis

Just as insulin exerts its effects on other organs and tissues, other organs interact with the pancreas to modulate insulin secretion (Figure 4). One of these interacting organs is the brain, which comprises the mutual brain–islet axis that interacts with the pancreas and vice versa. The pancreas is highly innervated with both, parasympathetic99,100 and sympathetic100,101 nerve fibers from the autonomic nervous system. At the same time, insulin receptors are widely distributed within the brain, including the hypothalamus, cerebral cortex, cerebellum102 and hippocampal formation103 in humans, as well as the olfactory and limbic areas,104,105 hypothalamus106—particularly the periventricular nucleus107 and the arcuate nucleus108,109—hippocampus and the choroid plexus105 in rat brains. Lesions in various brain regions were shown to affect pancreatic hormone secretion. The destruction of the ventromedial hypothalamus results not only in insulin hypersecretion110–112 due to loss of the ventromedial hypothalamus-mediated inhibitory impact on pancreatic β-cells113 but also in higher glucagon levels.111,112 Glucagon secretion may also be modulated by the hypothalamic brain-derived neurotrophic factor114 via efferent nerves.115 whereas the melanocortin system directly reduces basal insulin levels by
stimulating sympathetic nerve fibers via $\alpha$-adrenoceptors. Acting via $\alpha$-adrenoceptors, norepinephrine also inhibits insulin secretion, which is an important aspect of the fight-or-flight response. The neurotransmitter Neuropeptide Y (NPY), which is mainly expressed in the sympathetic nerve fibers of the autonomic nervous system, also blunts insulin release, and the loss of NPY’s inhibitory action results in elevated basal and glucose-stimulated insulin secretion as well as in increased islet mass. NPY binding to its GPCR $\gamma_1$ causes the activated $G_\alpha_i$ subunit to block adenylate cyclase activation, which in turn inhibits the cAMP pathway. Furthermore, the NPY-mediated inhibition was shown to be $G_{\beta\gamma}$- and Ca$^{2+}$-independent. In addition to the well-known insulin stimulator acetylcholine, which exerts its effects via M$_3$ muscarinic receptors, melanin concentrating hormone, vasoactive intestinal peptide (VIP), its close relative pituitary adenylate cyclase-activating polypeptide (PACAP) and gastrin-releasing peptide also promote insulin and, in the case of VIP and PACAP, glucagon release. The various neuropeptides exert their effects through various pathways, including the extracellular signal-regulated kinase (ERK)/Akt pathway, and modulation of Ca$^{2+}$-influx (melanin concentrating hormone), $\gamma$-muscarnic/\$beta$-adrenoceptors signaling, PI3K/PKC signaling and Ca$^{2+}$-mobilization from intracellular stores (gastrin-releasing peptide).

Figure 4 The interplay of the pancreas with the brain, liver, gut as well as adipose and muscle tissue. The pancreas interacts with the brain, liver, gut and adipose and muscle tissue in a highly sophisticated network via various hormones, neurotransmitters and cytokines. BDNF, brain-derived neurotrophic factor; CCK, cholecystokinin; GIP, glucose-dependent insulinotropic peptide; GLP-1, glucagon-like peptide 1; GRP, gastrin-releasing peptide; IL-6, Interleukin 6; MCH, melanin concentrating hormone; NPY, neuropeptide Y; PACAP, pituitary adenylate cyclase-activating polypeptide; POMC, pro-opiomelanocortin; VIP, vasoactive intestinal peptide.

Likewise, insulin release is stimulated by the so-called cephalic phase, which represents the conditioned reflex of increased hormone secretion, referred to as cephalic phase insulin response, even in the absence of nutrients/glucose as a trigger, such as when anticipating a meal, to prepare the organism to adequately respond to incoming nutrients. Moreover, cephalic phase insulin response is pivotal for ensuring normal postprandial glucose management. The neural mechanism underlying cephalic phase insulin response was found to include cholinergic and non-cholinergic processes as well as the dorsal vagal complex located in the medulla oblongata. Conversely, insulin released in response to a meal enters the brain via the blood–brain barrier to decrease food intake by stimulating hypothalamic pro-opiomelanocortin neurons and initiating the PI3K signaling pathway in these pro-opiomelanocortin neurons. In contrast to its pro-opiomelanocortin-stimulating action, insulin inhibits NPY expression in Agouti-related peptide (AgRP/NPY) neurons, which are known to secrete the orexigenic neuropeptides NPY and AgRP. Both, peripheral and central insulin signaling are impaired in obese or diabetic states.

The liver–islet axis
The second group represents the liver–islet axis. The liver has a key role in glucose homeostasis by storing (glycogenesis) or releasing (glycogenolysis/gluconeogenesis) glucose upon
interaction with insulin and glucagon, respectively. The binding of glucagon to its hepatic GPCR evokes the signaling cascade described under ‘External factors affecting pancreatic hormone secretion’, eventually resulting in the activation of PKA, which in turn stimulates two processes; one promotes glycogenolysis/gluconeogenesis and the other inhibits glycogenolysis/glycogenesis.155,156 Glycogenolysis is a multistep process that includes the PKA-mediated phosphorylation of phosphorylase kinase,157 cleavage of glucose-1-phosphate (G-1-P) from glycogen by activated glycogen phosphorylase a158 and the conversion of G-1-P into G-6-P,159 eventually resulting in phosphate and free glucose. Hepatic glycogenolysis is promoted by the PKA-mediated phosphorylation of the cAMP response element-binding protein, which in turn upregulates peroxisome proliferator-activated receptor-γ coactivator (PGC)-1.160 Together with the hepatocyte nuclear factor (HNF)-4, PGC-1 induces the transcription of phosphoenolpyruvate carboxykinase,161 which catalyzes the conversion of oxaloacetate into phosphoenolpyruvate, a rate-limiting step in gluconeogenesis. This is followed by reversed glycolysis, during which stimulation of the bifunctional PFK-2/FBPase-2 leads to both, enhanced gluconeogenesis through the abrogation of disabled fructose-1,6-bisphosphatase (FBPase)-1, which facilitates the successive conversion of substrates into G-6-P, and to suppressed glycolysis.162,163 Glycolysis is further inhibited by the PKA-mediated inactivation of pyruvate kinase,164–166 resulting in the production of glucose instead of pyruvate. In addition, glucagon was found to suppress pyruvate kinase gene expression as well as to enhance pyruvate kinase mRNA degradation.167,168 Finally, the PKA-induced inactivation of hepatic glycogen synthase169–171 decreases glycogen synthesis and concomitantly increases the hepatic glucose pool.

As glucagon’s opponent, insulin stimulates glycolysis via enhanced expression of the hepatic glucokinase gene,14,15 a key enzyme that converts glucose into G-6-P. This increase is mediated by the sterol regulatory element binding protein-1c172 through the PI3K pathway, which in turn activates glycogen synthase,18–20 The second liver-specific effect of insulin is to repress the expression of the phosphoenolpyruvate carboxykinase and G-6-Pase genes; the first by disrupting the association of cAMP response element-binding protein and RNA polymerase II with the phosphoenolpyruvate carboxykinase gene promoter,23 whereas G-6-P suppression requires PKBα/Akt and forkhead transcription factor (FOXO1).24,25 whose expression was shown to be diminished by the inhibition of GSK-3.26

It is not only insulin and glucagon acting on the liver; hepatocyte-derived factors conversely influence the pancreas and/or insulin secretion. Although HNF3β was proposed to be pivotal for the transcription of the pancreatic and duodenal homeobox 1 (pdx1 or insulin promoter factor 1 (IPF-1)) gene, a transcription factor regulating pancreatic development,173,174 its loss of HNF1α resulting in an almost abolished insulin secretion, likely due to a decreased response to intracellular calcium. These findings support the importance of HNF1α in maintaining β-cell function174 and its involvement in maturity-onset diabetes of the young (MODY3).177

The hepatokine betatrophin, also known as TD26, re-feeding induced fat and liver (RIFL), lipasin or angiopeptin-like (ANGPTL) 8, was first identified as a factor that drives β-cell proliferation and thus increases β-cell mass in a murine model of insulin resistance.178 Subsequent studies, however, did not reveal impairments in glucose homeostasis179 or β-cell expansion in Angptl8 knockout mice.180 Moreover, betatrophin does not have an effect on human β-cell replication, challenging its usefulness in diabetes therapy.181 This is substantiated by the fact that betatrophin levels are higher in T2DM patients,182–184 although they were lower in one study.185 However, this is likely to be due to technical issues.186

The gut–islet axis

Another important axis is the gut–islet axis. The gut releases various hormones upon nutrient ingestion, including GLP-1 and GIP, that bind to their respective receptors on pancreatic β-cells to potentiate insulin secretion, as described under ‘External factors affecting pancreatic hormone secretion’. Furthermore, both hormones exert pancreatic effects, such as GLP-1-stimulated insulin gene expression,77,187 incretin-induced β-cell neogenesis, proliferation,188–191 and survival,192 the prevention of β-cell apoptosis in general193,194 and in response to glucolipotoxicity.195 The extrapancreatic actions of GLP-1 include suppression of endogenous glucose production196/glycogenolysis,197 glucagon secretion,197,198 appetite,199,200 a delay in gastric emptying198,199 and improved β-cell insulin sensitivity199,201,202 and glucose disposal,203,204 whereas GIP positively affects lipid205–207 and bone metabolism.208–211 Thus, GLP-1 and GIP mediate insulin secretion and concomitantly, insulin modulates GIP212 and GLP-1 release; the latter occurring through the PI3K/Akt- and mitogen-activated protein kinase kinase (MAPKK or MEK)/ERK1/2 pathway.213 The importance of this interplay is also demonstrated by defective insulin responses and consequent glucose intolerance in GLP-1R−/− and GIPR−/− mice214–218 as well as in the pathogenesis of T2DM.219–223

In addition to incretins, there are the so-called decretins, namely limostatin and Neuromedin U (NmU), which are secreted during fasting to suppress insulin release. NmU, a (neuro)peptide that mediates the contraction of smooth muscles in the uterus (hence the "U") among others, was first isolated from the pig spinal cord.224 Further mRNA expression studies, however, revealed NmU to be highly expressed in the gastrointestinal (GI) tract with the highest levels found in the upper GI, that is, duodenum and jejunum.225,226 Within the GI structure, NmU is mainly located in submucosal and myenteric cells,227,228 indicating its possible involvement in the neuronal control of GI function.229 In addition to this, NmU is likely to regulate insulin secretion; the G-protein-coupled NmU receptor 1 (NmUR1) is expressed in pancreatic islets and its simulation dose dependently decreased insulin release.230,231
The underlying mechanism involves the simultaneous release of somatostatin—a known modulator of insulin secretion—upon NmUR1 activation. A recent study showed that the peptide hormone limostatin, which is expressed in Drosophila melanogaster, also reduces insulin secretion and its absence caused hyperinsulinemia, hypoglycemia and obesity. Moreover, knockdown of the fly NmUR orthologue not only reproducibly expressed the consequences of limostatin deficiency but also diminished its insulin-suppressing ability. Limostatin release is initiated by food depletion and hence may represent a novel mechanism for modulating insulin secretion during fasting.

Other gastrointestinal hormones that interact with the pancreas are gastrin and cholecystokinin (CCK). Gastrin, which is secreted from G-cells in the stomach and duodenum, acts as an islet growth factor, together with transforming growth factor-α, by promoting differentiation of ductular precursor cells and β-cell neogenesis as well as by enhancing the islet mass from transdifferentiated exocrine pancreatic tissue. Furthermore, it induces the expression of glucagon genes in α-cells. Along the same lines, CCK, which is synthesized and released from duodenal I-cells, potentiates basal, glucose- and amino acid-induced insulin secretion, and augments glucagon secretion. The pivotal role of CCK in modulating glucose homeostasis is reflected in postprandial hyperglycemia, which is due to reduced CCK plasma levels in noninsulin-dependent diabetes mellitus.

Another important factor that is related to metabolic disorders such as obesity, T2DM and type 1 DM (T1DM) is the gut microbiota. Obesity, T2DM and T1DM patients display alterations in the composition of their microbiota that may initiate and/or promote the respective disorder. Recent findings linked an aberrant microbiome, which is generally represented by diminished diversity, including fewer butyrate-producing (butyrate was shown to trigger mucin production and hence gut integrity) and mucin-degrading bacteria, to the development of autoimmunity in T1DM. An altered microbiota composition may also contribute to obesity as well as to T2DM and ‘correction’ by antibiotics, probiotics or prebiotics, the last of which causing a short-chain FFA-stimulated increase in GLP-1 may improve the disease condition.

The adipocytes/myocytes–islet axis

On one hand, insulin’s interplay with adipose and muscle tissue is broadly based on facilitating insulin-dependent glucose uptake through the glucose transporter 4 (GLUT4). On the other hand, adipokines and myokines secreted from the adipose and muscle tissue, respectively, modulate insulin release. As part of the so-called adipoinisular axis, leptin, the most famous adipokine, mainly acts on its receptors in the hypothalamic arcuate nucleus to inhibit food intake and control whole body homeostasis. However, leptin receptor (Ob-R) mRNA expression was also observed in pancreatic islets and its stimulation caused a reduction in insulin secretion due to the activation of K channels, which in turn prevented Ca-influx and the subsequent signaling pathway. Furthermore, leptin was shown to suppress insulin gene expression, representing a negative feedback loop. Conversely, insulin enhances ob gene expression and leptin secretion. Likewise, insulin modulates the expression of adiponectin, another well-known adipokine, the abundance of its receptor in adipose and muscle tissue as well as its secretion. Adiponectin is not only involved in glucose and fatty acid metabolism but it also forestalls β-cell apoptosis and induces insulin gene expression and release; the latter was mediated by the ERK/ Akt pathway in one study and by the AMPK pathway in another study. Other adipokines, such as apelin, chemerin, omentin, resistin and visfatin were also shown to directly interact with insulin, whereas retinol-binding protein 4, tumor necrosis factor-α and vasp are related to insulin in an indirect manner. In addition to adipokine secretion by adipocytes, myocytes release cytokines, which are referred to as myokines. Fibroblast growth factor-21 is a widely expressed protein with a broad mode of action, including the regulation of carbohydrate and fatty acid metabolism and may be considered as a myokine due to its secretion from muscle cells. Fibroblast growth factor-21 is regulated by insulin through the PI3K/Akt1 signaling pathway. Interleukin (IL)-6, which is both an adipokine and myokine, was shown to influence the pancreas by controlling the expression of pro-glucagon mRNA as well as glucagon secretion. It also increases α-cell proliferation and islet mass while protecting the pancreas from metabolic stress-induced apoptosis. Furthermore, IL-6 increased GLP-1 production from proglucagon in pancreatic α-cells and its secretion from α-cells and intestinal L-cells, eventually resulting in a GLP-1-mediated increase in insulin secretion.

MODULATING INSULIN SECRETION AS A MEANS OF DIABETES THERAPY

Due to the worldwide, still spreading epidemic of T2DM, there is an urgent need for (new) anti-diabetic drugs and therapies that are more effective and have fewer side effects. Currently, the most commonly used drugs can be classified into agents that enhance insulin secretion (secretagogues such as sulfonylureas (SUs) and incretin mimetics), sensitize the target organs of insulin (for example, metformin from the class of biguanides or thiazolidinediones), or reduce glucose absorption from the gastrointestinal tract (inhibitors of gastrointestinal α-glucosidase). Different therapies address different problems and stages of T2DM and may be prescribed in combination to exert synergistic effects.

Sulfonylureas

A-glucosidase inhibitors and sensitizers do not target the pancreas or insulin secretion itself but instead target the upstream (slowed intestinal glucose absorption) or downstream (improved insulin sensitivity) processes. In contrast, insulin secretagogues directly modulate insulin release. The SUs are the...
first broadly applied oral anti-hyperglycemic drugs. To date, there are two generations of agents: acetohexamide, chlorpropamide, tolazamide and tobutamidine, which constitute the first generation and glibenclamide/glyburide, gliclazide, glimepiride, glipizide and gliquidone, which comprise the second generation. First-generation SUs are rarely used these days since tobutamidine intake was associated with an increase in lethal cardiac events.\(^{290,291}\) More importantly, the second-generation SUs are more potent due to modifications in their side chains’ structure, resulting in improved SUR-affinity, accompanied by lower effective plasma levels, which in turn may reduce undesirable drug-protein interactions.

All SUs share a central SU backbone but differ in their side chains. Despite having different pharmacokinetics, they work in the same way, namely by triggering endogenous insulin release by blocking \(K_{\text{ATP}}\)-channels and hence activating the insulin signaling pathway. More precisely, SUs bind to the sulfonylurea receptor (SUR) subunit of the \(K_{\text{ATP}}\)-channel with high affinity.\(^{292,293}\) SUR, together with the pore-forming subunit Kir6.x, forms a hetero-octameric complex consisting of four inner Kir6.x subunits surrounded by four SUR subunits (4:4 stoichiometry).\(^{294,295}\) Moreover, different isoforms of the two subunits are expressed, depending on the tissue-specific expression of the \(K_{\text{ATP}}\)-channels: SUR1 and Kir6.2 are expressed in the pancreas and brain,\(^{296}\) Kir6.2 and SUR2A are expressed in the heart and skeletal muscle,\(^{297}\) while SUR2B is expressed in the brain and smooth muscle,\(^{298}\) and Kir6.1 and SUR2B are expressed in vascular smooth muscle.\(^{299}\) Although SUs bind to both, SURs and Kir6.2, the interactions with the latter are of low affinity\(^{300,301}\) and hence only SUR-interacting agents are used for diabetes treatment. In addition to their mode of action as inhibitors of \(K_{\text{ATP}}\)-channels, SUs were shown to improve glucose uptake into insulin-dependent tissues and glucose disposal as well as to reduce hepatic glycogenolysis/gluconeogenesis.\(^{302–304}\)

In contrast to SUs inactivating the \(K_{\text{ATP}}\)-channels by binding to the SUR1 subunit, ATP closes them by interacting with Kir6.2.\(^{305}\) Moreover, while the binding of only one ATP molecule is sufficient to completely close the channel,\(^{306}\) inhibition by SUs is incomplete as the channel might still open even when SUs are bound to SUR1.\(^{299}\) Nonetheless, second-generation SUs reduce the glycated hemoglobin or HbA\(_{1C}\), which represent the average plasma glucose concentrations over time and thus serve as a diagnostic measure for diabetes mellitus, by 1.0–2.0%. In addition to the weight gain attributed to the anabolic effects of increased insulin secretion, the main side effect of SUs is hypoglycemia\(^{307,308}\) due to excess circulating insulin levels and due to the fact that SUs evoke insulin secretion in a glucose-independent manner.\(^{309}\)

Although they are not SUs per se, meglitinides, that is, repaglinide and nateglinide, share their mode of action of inhibiting \(K_{\text{ATP}}\)-channels.\(^{310}\) However, meglitinides and some of the second-generation SUs, for example, glibenclamide, interact with both, the SUR1 and the SUR2A or B isoforms.\(^{311}\) Despite the possible disadvantage of this generalized binding that may cause undesirable effects on other \(K_{\text{ATP}}\)-channel types, for example, those in the heart,\(^{312}\) meglitinides, namely nateglinide, have an earlier onset of action and a faster dissociation rate from the sulfonylurea receptor,\(^{313–315}\) resulting in a diminished risk of hypoglycemia.\(^{316}\) Like SUs, meglitinides also cause weight gain.\(^{317,318}\)

**Incretin mimetics**

Another group of insulin secretagogues is comprised of the incretins GLP-1 and GIP. As both incretins are rapidly inactivated by the enzyme dipeptidyl peptidase IV (DPP-IV),\(^{319}\) their application in T2DM treatment focuses on modified analogues\(^{320–325}\) or receptor agonists, including the well-known, short-acting exenatide.\(^{326–328}\) The long-lasting agonists exenatide LAR,\(^{329,330}\) liraglutide\(^{331,332}\) and lixisenatide\(^{333–335}\) are currently under investigation. However, based on the lipogenic properties\(^{305–307}\) of GIP, insufficient insulin-potentiating effects in T2DM patients\(^{220,336}\) and a possible worsening effect by GIP,\(^{337,338}\) the focus is on GLP-1 analogues/receptor agonists for T2DM treatment. By acting on its receptor, GLP-1 induces the signaling cascade described under ‘External factors affecting pancreatic hormone secretion’, resulting in its main effect: potentiating insulin secretion. In addition to reducing the HbA\(_{1C}\) levels, GLP-1 analogues/receptor agonists promote weight loss and, more importantly, do not evoke hypoglycemia, as do SUs,\(^{326–334}\) due to the glucose-dependent mode of action and the self-regulating mechanism of GLP-1.\(^{338–340}\) When blood glucose levels are lowered to physiological levels, GLP-1 is incapable of enhancing insulin secretion, thereby preventing hypoglycemia.\(^{340}\)

In addition, GLP-1 (analogues/receptor agonists) exerts further pancreatic and extrapancreatic actions, as mentioned under ‘Interplay between the pancreatic islets and other organs’. Although GLP-1 (analogues/receptor agonists) exhibits some minor side effects, including nausea, vomiting or gastrointestinal impairments,\(^{326–335}\) the beneficial properties outweigh the negative effects, and thus, GLP-1 is a promising anti-diabetic agent.

**Insulin sensitizers**

Metformin, which is generally the most widely used first-line anti-diabetic medication,\(^{341}\) is a so-called (insulin) sensitizer. It not only diminishes hepatic glucose output due to glycogenolysis/gluconeogenesis\(^{342}\) but it also enhances glucose uptake into peripheral tissues, such as skeletal muscle, by activating 5′-adenosine monophosphate-activated protein kinase (AMPK-α2).\(^{343}\) Furthermore, it supports weight loss\(^{344}\) by reducing food consumption.\(^{345}\) With respect to its effects on β-cell function, metformin was shown to increase insulin gene expression,\(^{346}\) possibly by nuclear accumulation of pdx1 and its subsequently improved DNA-binding activity.\(^{347}\) Interestingly, metformin exerts opposing effects on β-cell proliferation and/or apoptosis; on the one hand, it suppresses β-cell proliferation and enhances apoptosis through an AMPK-dependent and autophagy-mediated mechanism\(^{348}\) following the metformin-induced activation of c-Jun-N-terminal kinase and caspase-3.\(^{349}\) On the other hand, metformin reduces
Caspase-3- and -8-mediated apoptosis in isolated islets from T2DM patients and protects against lipotoxicity-induced β-cell defects.

The other members of the sensitizer group include the thiazolidinediones (or glitazones). Currently, only pioglitazone is available; troglitazone was withdrawn from the market in 2000 and rosiglitazone was withdrawn in 2010 due to liver toxicity, drug-induced hepatitis and the increased risk of cardiovascular events, respectively. Their mode of action involves activation of the peroxisome proliferator-activated receptor (PPARγ), a nuclear transcription factor that is highly expressed in adipose tissue, and the subsequent regulation of genes that are involved in glucose and fat metabolism. By promoting lipogenesis, FFAs are removed from the blood, whereupon cells become dependent on glucose as an energy substrate. However, enhanced lipogenesis also leads to the weight gain observed in thiazolidinedione-treated T2DM patients. In contrast to metformin, pioglitazone prevents (oxidative stress-induced) apoptosis by decreasing the expression of apoptosis-promoting genes, while increasing anti-apoptotic and anti-oxidative gene expression. However, this may depend on the disease state. Furthermore, pioglitazone increases β-cell mass by upregulating cell differentiation/proliferation genes. Although they have partially different modes of action, both groups of sensitizers cause a reduction in the HbA1c level by 1.5–2.0%.

**A-glucosidase inhibitors**

A-glucosidase inhibitors, such as acarbose, miglitol and voglibose, not only decelerate the breakdown of starch into glucose in the small intestine but also decrease its bioavailability, resulting in reduced levels of glucose entering the blood stream and hence attenuated postprandial glucose excursions. In addition, they support weight loss and ameliorate blood pressure, insulin sensitivity and triglyceride levels. Similar to pioglitazone, α-glucosidase inhibitors attenuate reductions in β-cell mass, which may delay the onset of diabetes. As α-glucosidase inhibitors only mildly reduce HbA1c levels (0.5–1.0%), they are usually only used in the early stage of T2DM, that is, impaired glucose tolerance or in combination with other drugs.

**CONCLUSIONS AND OUTLOOK**

The pancreas has key roles in maintaining normal blood glucose levels by producing and releasing insulin and glucagon. The authors declare no conflict of interest.

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1. Chandra R, Liddle RA. Neural and hormonal regulation of pancreatic secretion. *Curr Opin Gastroenterol* 2009; 25: 441–446.
2. Brissova M, Fowler MJ, Nicholson WE, Chu A, Hirshberg B, Harlan DM et al. Assessment of human pancreatic islet architecture and composition by laser scanning confocal microscopy. *J Histochem Cytochem* 2005; 53: 1087–1097.
3. Katsura G, Asakawa A, Inui A. Roles of pancreatic polypeptide Snapin, the t-SNARE SNAP-25, cyclin-dependent kinase (Cdk) 5, ryanodine receptor (RyR) 2, the nucleotide exchange factor and intracellular cAMP sensor Epac2, mammalian uncoordinated proteins (munc)13-00, and munc18-04 as well as the Ras-related proteins (Rab) 3A and 27A.403

**CONFLICT OF INTEREST**

The authors declare no conflict of interest.
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Cabrera O, Berman DM, Kenyon NS, Ricordi C, Berggren PO, Caicedo A. The unique cytoarchitecture of human pancreatic islets has implications for islet cell function. Proc Natl Acad Sci USA 2006; 103: 2334–2339.

Freychet L, Rizkalla SW, Desplanque N, Basdevant A, Zirinis P, Tchobroutsky G et al. Effect of intranasal glucagon on blood glucose levels in healthy subjects and hypoglycaemic patients with insulin-dependent diabetes. Lancet 1988; 1: 1364–1366.

Komatsu M, Takei M, Ishii H, Sato Y. Glucose-stimulated insulin secretion: a new perspective. J Diabetes Investig 2013; 4: 511–516.

Khan AH, Pessin JE. Insulin regulation of glucose uptake: a complex interplay of intracellular signalling pathways. Diabetologia 2002; 45: 1475–1483.

Kohn AD, Summers SA, Mauvais-Jarvis F, Lowell BB. Expression of a newcomer insulin granule exocytosis and compound fusion in pancreatic beta-cells. Diabetes 2013; 62: 2416–2428.

Voets T, Toonen RF, Brien EC, de Wit H, Moser T, Retting J et al. Munc18-1 promotes large dense-core vesicle docking. Neuron 2001; 31: 581–591.

Buck D, Zhang Z, Boulton AJW, Lacy T, Bode C. Calcitonin gene-related peptidergic antagonism of islet beta cell function. Diabetes 2011; 60: 783–793.

Streeter RS, Svitak CA, Chapman S, Greenbaum LE, Taub R, O’Brien RM. A multicomponent insulin response sequence mediates a strong repression of mouse glucose-6-phosphate gene transcription by insulin. J Biol Chem 1997; 272: 11698–11701.

Ducam DT, Wallner-Lee ME, Sears R, Sealy L, Granner DK. Insulin inhibits hepatocellular glucose production by utilizing liver-enriched transcriptional inhibitory protein to disrupt the association of CREQ-binding protein and RNA polymerase II with the phosphoenolpyruvate carboxykinase gene promoter. J Biol Chem 2002; 277: 32234–32242.

Nakae J, Kitamura T, Silver DL, Accili D. The forkhead transcription factor FoxO1 (Fkh1) confers insulin sensitivity onto glucose-6-phosphatase expression. J Clin Invest 2001; 108: 1359–1367.

Schmoll D, Walker KS, Alessi DR, Gremler R, Burchell A, Guo S et al. Regulation of glucose-6-phosphate gene expression by protein kinase B (Akt) in 3T3-L1 adipocytes stimulates glucose uptake and transporter 4 translocation. J Biol Chem 1996; 271: 31372–31378.

Zisman A, Peroni OD, Abel ED, Michael MD, Mauvais-Jarvis F, Lowell BB. Targeted disruption of the glucose transporter 4 selectively in muscle and liver leads to diabetes. Cell 2004; 116: 563–574.

McNair PG, Harte AL, Anderson LA, Green A, Smith SA, Holder JC et al. Insulin and rosiglitazone regulation of lipolysis and lipogenesis in human adipose tissue in vitro. Diabetes 2002; 51: 1493–1498.
Pancratic regulation of glucose homeostasis

PV Röder et al.

53 Sadana R, Dessauer CW. Physiological roles for G protein-regulated adenyl cyclase: insights from knockout and overexpression studies. *Neurosignals* 2009; 17: 5–22.

54 Das R, Esposito V, Abu-Abed M, Anand GS, Taylor SS, Melacini G. cAMP activation of PKA defines an ancient signaling mechanism. *Proc Natl Acad Sci USA* 2007; 104: 93–98.

55 Li S, Tsalkova T, White MA, Mei FC, Liu T, Wang D et al. Mechanism of intracellular CAMP sensor Epac2 activation: CAMP-induced conformational changes identified by amide hydrogen/deuterium exchange mass spectrometry (DXMS). *J Biol Chem* 2011; 286: 17889–17897.

56 Leech CA, Chepurny OG, Chepurny GG, Leech CA, Roe MW, Dzhura E et al. Epac2-dependent mobilization of intracellular Ca(2+) by glucagon-like peptide-1 receptor agonist exendin-4 is disrupted in beta-cells of phospholipase C-epsilon knockout mice. *J Physiol* 2010; 588(Pt 24): 4871–4889.

57 Shibasaki T, Takahashi H, Miki T, Sunaga Y, Matsumura K, Yamanaka M et al. Essential role of Epac2/Rap1 signaling in regulation of insulin granule dynamics by CAMP. *Proc Natl Acad Sci USA* 2007; 104: 19333–19338.

58 Beguin P, Nagashima K, Nishimura M, Gnoi S, Seino S. PKA-mediated phosphorylation of the human K(ATP) channel: separate roles of Kir6.2 and SUR1 subunit phosphorylation. *EMBO J* 1999; 18: 4722–4732.

59 Kanno T, Suga S, Wu J, Kimura M, Wakui M. Intracellular cAMP potentiates voltage-dependent activation of L-type Ca(2+) channels in rat islet beta-cells. *Pflugers Arch* 1998; 435: 578–580.

60 Safary H, Haase H, Kramer U, Bihlmayer A, Roenfeldt M, Ammon HP et al. L-type calcium channels in insulin-secreting cells: biochemical characterization and phosphorylation in RINm5F cells. *Mol Endocrinol* 1997; 11: 619–629.

61 Wan QF, Dong Y, Yang H, Lou X, Ding J, Xu T. Protein kinase activation increases insulin secretion by sensitizing the secretory machinery to Ca(2+). *J Gen Physiol* 2004; 124: 653–662.

62 Renstrom E, Eliasson L, Ronsmann P. Protein kinase A-dependent and -independent stimulation of exocytosis by CAMP in mouse pancreatic B-cells. *J Physiol* 1997; 502(Pt 1): 105–118.

63 Reimann F, Habib AM, Tolhurst G, Parker HE, Rogers GJ, Gribble FM. Glucose sensing in L cells: a primary cell study. *Cell Metab* 2008; 8: 532–539.

64 Parker HE, Habib AM, Rogers GJ, Gribble FM, Reimann F. GLUTag-dependent secretion of glucagon-like insulinotropic polypeptide from primary murine K cells. *Diabetologia* 2009; 52: 289–298.

65 Elliott RM, Morgan LM, Tredger JA, Deacon S, Wright J, Marks V. Glucagon-like peptide-1 (7-36)amide and glucagon-dependent insulinotropic polypeptide secretion in response to nutrient ingestion in man: acute post-prandial and 24-h secretion patterns. *J Endocrinol* 1993; 138: 159–166.

66 Kuhre RE, Gribble FM, Hartmann B, Reimann F, Windelov JA, Rehfeld JF et al. Fructose stimulates GLP-1 but not GIP secretion in mice, rats, and humans. *Am J Physiol Gastrointest Liver Physiol* 2014; 306: G622–G630.

67 Reimann F, Williams L, da Silva Xavier G, Rutter GA, Gribble FM. Glutamine potently stimulates glucagon-like peptide-1 secretion from GLUTag cells. *Diabetologia* 2004; 47: 1592–1601.

68 Tolhurst G, Heffron H, Lam YS, Parker HE, Habib AM, Diakogiannaki E et al. Short-chain fatty acids stimulate glucagon-like peptide-1 secretion via the G-protein-coupled receptor FFAR2. *Diabetes* 2012; 61: 364–371.

69 Hirase A, Tsumaya K, Awaji T, Katsuma S, Adachi T, Yamada M et al. Free fatty acids regulate gut incretin glucagon-like peptide-1 secretion through GPR120. *Nat Med* 2005; 11: 90–94.

70 Schauder P, Brown JC, Frechins H, Creutzfeldt W. Gastric inhibitory polypeptide: effect on glucose-induced insulin release from isolated rat pancreatic islets in vitro. *Diabetologia* 1975; 11: 483–484.

71 Ribalet B, Ciani S, Eddlestone GT. ATP mediates both activation and control of islet insulin secretion by glucagon-like peptide-1. *Vitam Horm* 2010; 84: 279–302.

72 Kang G, Joseph JW, Chepurny OG, Monaco M, Wheeler MB, Bos JL et al. Epac-selective cAMP analog 8-pCPT-2′-O-Me-cAMP as a stimulus for Ca(2+)-induced Ca(2+) release and exocytosis in pancreatic beta-cells. *J Biol Chem* 2003; 278: 8279–8285.

73 Dzhura I, Chepurny OG, Kelley GG, Leech CA, Roe MW, Dzhura E et al. Epac2-dependent mobilization of intracellular Ca(2+) by glucagon-like peptide-1 receptor agonist exendin-4 is disrupted in beta-cells of phospholipase C-epsilon knockout mice. *J Physiol* 2010; 588(Pt 24): 4871–4889.
94 Itahi Y, Kawamata Y, Harada M, Kobayashi M, Fujii R, Fukusumi S et al. Free fatty acids regulate insulin secretion from pancreatic beta cells through GPR40. Nature 2003; 422: 173–176.

95 Ximenes HM, Hirate AE, Rocha MS, Curi R, Carpinelli AR. Propionate inhibits glucose-induced insulin secretion in isolated rat pancreatic islets. Cell Biochem Funct 2007; 25: 173–178.

96 Porte D Jr, Williams RH. Inhibition of insulin release by norepinephrine in man. Science 1966; 152: 1248–1250.

97 Peterhoff M, Sieg A, Brede M, Chao CM, Hein L, Ullrich S. Inhibition of insulin secretion via distinct signaling pathways in alpha2-adrenoceptor knockout mice. Eur J Endocrinol 2003; 149: 343–350.

98 Porte D Jr. A receptor mechanism for the inhibition of insulin release by epinephrine in man. J Clin Invest 1967; 46: 86–94.

99 Young WS 3rd. Periventricular hypothalamic cells in the rat brain contain receptor mRNA in rat brain by in situ hybridization. Endocrinology 1990; 127: 3234–3236.

100 Borden P, Houtz J, Leach SD, Kuruvilla R. Sympathetic innervation during development is necessary for pancreatic islet architecture and functional maturation. Cell Rep 2013; 4: 287–301.

101 Hopkins DF, Williams G. Insulin receptors are widely distributed in human brain and bind human and porcine insulin with equal affinity. Diabet Med 1991; 8: 990–995.

102 Hol L, Yermul N, Kralj V, Kaste L, Zhao R, Haroutunian V et al. Insulin receptor expression and activity in the brains of non diabetic sporadic Alzheimer's disease cases. Int J Alzheimers Dis 2012; 2012: 321280.

103 Hill JM, Lesniak MA, Pert CB, Roth J. Autoradiographic localization of insulin receptors in rat brain: prominence in olfactory and limbic areas. Neuroscience 1986; 17: 1127–1138.

104 Marks JL, Porte D Jr, Stahl WL, Baskin DG. Localization of insulin receptor mRNA in rat brain by in situ hybridization. Endocrinology 1990; 127: 3234–3236.

105 Obici S, Feng Z, Kirkland G, Baskin DG, Rossetti L. Decreasing hypothalamic insulin receptors causes hyperphagia and insulin resistance in rats. Nat Neurosci 2002; 5: 566–572.

106 Young WS 3rd. Periventricular hypothalamic cells in the rat brain contain insulin mRNA. Neuropeptides 1986; 8: 93–97.

107 Mirshamsi S, Laidlaw HA, Ning K, Anderson E, Burgess LA, Gray A et al. Leptin and insulin stimulation of signaling pathways in arcuate nucleus neurons: PI3K dependent action and reactivation and ketotrophic channel activation. BMC Neurosci 2004; 5: 54.

108 Wang R, Liu X, Hengste ST, Dunn-Mellon AA, Levin BE, Wang W et al. The regulation of glucose-excited neurons in the hypothalamic arcuate nucleus by glucose and feeding-related peptides. Diabetes 2004; 53: 1959–1965.

109 Berthoud HR, Jeannaud B. Acute hyperinsulinemia and its reversal by vagotomy after lesions of the ventromedial hypothalamus in the rat. Gastroenterology 1987; 92: 138–144.

110 Rohner-Jeanrenaud F, Jeannraud B. Consequences of ventromedial hypothalamic lesions upon insulin and glucagon secretion by subsequently isolated perfused pancreas in the rat. J Clin Invest 1980; 65: 902–910.

111 Goto Y, Carpenter RG, Berelowitz M, Frohman LA. Effect of ventromedial hypothalamic lesions upon the secretion of somatostatin, insulin, and glucagon by the perfused rat pancreas. Metabolism 1980; 29: 986–990.

112 Dorner F, Dufour AC, Kanakash C, Le Marchand Y, Ruff KB, Jeannaud B. Immediate effect of lesion of the ventromedial hypothalamic area upon glucose-induced insulin secretion in anaesthetized rats. Diabetologia 1977; 13: 239–242.

113 Cort DI, Wurtz ST, Ikariishi T, Soda S, Maruyama S, Kamishita T et al. Brain-derived neurotrophic factor modulates glucagon secretion from pancreatic alpha cells: its contribution to glucose metabolism. Diabetes Obes Metab 2003; 5: 27–37.

114 Gotoh K, Masaki T, Chiba S, Ando H, Fujikura K, Shimakami T et al. Hypothalamic brain-derived neurotrophic factor regulates glucagon secretion mediated by pancreatic efferent nerves. J Neuroendocrinol 2013; 25: 302–311.

115 Fan W, Dinulescu DM, Butler AA, Zhou J, Marks DL, Cone RD. The central melanocortin system can directly regulate serum insulin levels. Endocrinology 2000; 141: 3072–3079.
140 Woods SC, Stein LJ, McKay LD, Porte D Jr. Suppression of food intake by intravenous nutrients and insulin in the baboon. Am J Physiol 1984; 247 (2 Pt 2): R393–R401.

141 Benoit SC, Air EL, Coolsen LM, Strauss R, Jackman A, Clegg DJ et al. The catabolic action of insulin in the brain is mediated by melanocortins. J Neurosci 2002; 22: 9048–9052.

142 Niswender KD, Morrison CD, Clegg DJ, Olson R, Baskin DG, Myers MG Jr et al. Insulin activation of phosphatidylinositol 3-kinase in the hypothalamic arcuate nucleus: a key mediator of insulin-induced anorexia. Diabetes 2003; 52: 227–231.

143 Xu AW, Kaelin CB, Takeda K, Akira S, Schwartz MW, Barsh GS. PI3K integrates the action of insulin and leptin on hypothalamic neurons. J Clin Invest 2005; 115: 951–958.

144 Schwartz MW, Sipols AJ, Marks JL, Sanacora G, White JD, Scheurink AJ et al. Inhibition of hypothalamic neuropeptide Y gene expression by insulin. Endocrinology 1992; 130: 3608–3616.

145 Flood JF, Morley JE. Increased food intake by neuropeptide Y is due to an increased motivation to eat. Peptides 1991; 12: 1329–1332.

146 Morley JE, Hernandez EN, Flood JF. Neuropeptide Y increases food intake in mice. Am J Physiol 1987; 253(2 Pt 2): R516–R522.

147 Aiston S, Coghlan MP, Agius L. Inactivation of phosphorylase is a major component of the mechanism by which insulin stimulates hepatic glycogen synthesis in vivo. Endocrinology 1998; 139: 4428–4431.

148 Schwartz MW, Marks JL, Sipols AJ, Baskin DG, Myers MG Jr et al. Central insulin administration reduces neuropeptide Y mRNA expression in the arcuate nucleus of food-deprived lean (Fa/Fa) but not obese (fa/fa) Zucker rats. Endocrinology 1991; 128: 2645–2647.

149 Carvalheira JB, Ribeiro EB, Araujo EP, Guimaraes RB, Telles MM, Torsoni M et al. Selective impairment of insulin signalling in the hypothalamus of obese Zucker rats. Diabetologia 2003; 46: 1629–1640.

150 Ikeda H, West DB, Pustek JJ, Figlewicz DP, Greenwood MR, Porte D Jr et al. Intravenricular insulin reduces food intake and body weight of lean but not obese Zucker rats. Appetite 1986; 7: 381–386.

151 Obici S, Zhang BB, Karkanias G, Rosetti L. Hypothalamic insulin signaling is required for inhibition of glucose production. Nat Med 2002; 8: 1376–1382.

152 Gelling RW, Morton GW, Morrison CD, Niswender KD, Myers MG Jr, Rhodes CJ et al. Insulin action in the brain contributes to glucose lowering during insulin treatment of diabetes. Cell Metab 2006; 3: 67–73.

153 Jiang G, Zhang BB. Glucagon and regulation of glucose metabolism. Am J Physiol Endocrinol Metab 2003; 284: E671–E678.

154 Feliu JE, Hue L, Hers HG. Hormonal control of pyruvate kinase activity and of gluconeogenesis in isolated hepatocytes. Proc Natl Acad Sci USA 1976; 73: 2762–2766.

155 De Wulf H, Hers HG. The role of glucose, glucagon and glucocorticoids in the regulation of liver glycogen synthesis. Eur J Biochem 1968; 6: 558–564.

156 Herzig S, Long F, Jhala US, Hedrick S, Quinn R, Bauer A et al. CREB regulates hepatic gluconeogenesis through the coactivator PGC-1. Nature 2001; 413: 179–183.

157 Yoon JC, Puigserver P, Chen G, Donovan J, Wu Z, Rhee J et al. CREB regulates hepatic gluconeogenesis through the transcriptional coactivator PGC-1. Nature 2001; 413: 131–138.

158 Pikis SJ, El-Maghrabi MR, McGrane M, Pikis J, Claus TH. Regulation by glucagon of hepatic pyruvate kinase, 6-phosphofructo 1-kinase, and fructose-1,6-bisphosphatase. Fed Proc 1982; 41: 2623–2628.

159 Gao H, Leary JA. Kinetic measurements of phosphoglucomutase by direct analysis of glucose-1-phosphate and glucose-6-phosphate using ion/molecule reactions and Fourier transform ion cyclotron resonance mass spectrometry. Anal Biochem 2004; 329: 269–275.

160 Herzog S, Long F, Jhala US, Hedrick S, Quinn R, Bauer A et al. CREB regulates hepatic gluconeogenesis through the coactivator PGC-1. Nature 2001; 413: 179–183.

161 Vaulont S, Munnich A, Decaux JF, Kahn A. Transcriptional and post-transcriptional regulation of L-type pyruvate kinase gene expression in rat liver. J Biol Chem 1986; 261: 7621–7625.

162 Fu Z, Berhane F, Fite A, Seyoum B, Abou-Samra AB, Zhang R. Elevated circulating lipasin/betatrophin in human type 2 diabetes and obesity. Sci Rep 2014; 4: 5013.
Glucagon-like peptide-1 induces pancreatic beta-cell proliferation via transactivation of the epidermal growth factor receptor. Diabetes 2003; 52: 124–132.

190 Buteau J, Foisy S, Joly E, Prentki M. Glucagon-like peptide-1 induces cell proliferation and pancreatic-duodenal homeobox-1 expression and increases endocrine cell mass in the pancreas of old, glucose-intolerant rats. Endocrinology 2000; 141: 4600–4605.

191 Trumper A, Trumper K, Trusheim H, Arnold R, McIntosh CH. Glucose-dependent insulinotropic polypeptide is a growth factor for beta cells. J Biol Chem 2002; 277: 37088–37097.

192 Kim SJ, Winter K, Nian C, Tsuneoka M, Koda Y, McIntosh CH. Glucose-dependent insulinotropic polypeptide (GIP) stimulation of pancreatic beta-cell survival is dependent upon phosphatidylinositol 3-kinase (PI3K)/protein kinase B (PKB) signaling, inactivation of the forkhead transcription factor Foxo1, and down-regulation of bax expression. J Biol Chem 2003; 278: 471–478.

193 Li Y, Hansotia T, Yusta B, Ris F, Halban PA, Drucker DJ. Glucagon-like peptide-1 receptor signaling modulates beta cell apoptosis. J Biol Chem 2003; 278: 471–478.

194 Trumper A, Trumper K, Horsch D. Mechanisms of mitogenic and anti-apoptotic signaling by glucagon-dependent insulinotropic polypeptide in beta(INS-1) cells. J Endocrinol 2002; 174: 233–246.

195 Buteau J, El-Assaad W, Rhodes CJ, Rosenberg L, Joly E, Prentki M. Glucagon-like peptide-1 prevents beta cell glucolipotoxicity. Diabetologia 2004; 47: 806–815.

196 Prigeon RL, Quddusi S, Paty B, D’Alessio DA. Suppression of glucose production by GLP-1 independent of islet function: a novel extrapancreatic effect. Am J Physiol Endocrinol Metab 2003; 285: E701–E707.

197 Degn KB, Juul CB, Sturis J, Jakobsen G, Brock B, Chandramouli V et al. One week’s treatment with the long-acting glucagon-like peptide 1 derivative liraglutide (NN2211) markedly improves 24-h glycaemia and alpha- and beta-cell function and reduces endogenous glucose release in patients with type 2 diabetes. Diabetes 2004; 53: 1187–1194.

198 Wills B, Werner J, Holst JJ, Orskov F, Creutzfeldt W, Nauck MA. Gastric emptying, glucose responses, and insulin secretion after a liquid test meal: effects of exogenous glucagon-like peptide-1 (GLP-1)-1 to 36 amide in type 2 (noninsulin-dependent) diabetic patients. J Clin Endocrinol Metab 1996; 81: 327–332.

199 Zander M, Madsbad S, Madsen JL, Holst JJ. Effect of 6-week course of glucagon-like peptide 1 on glycemic control, insulin sensitivity, and beta-cell function in type 2 diabetes: a parallel-group study. Lancet 2002; 359: 824–830.

200 Gutzwiller JP, Drew J, Goke B, Schmidt H, Rohrer B, Leraide J et al. Glucagon-like peptide-1 promotes satiety and reduces food intake in patients with diabetes mellitus type 2. Am J Physiol 1999; 276 (Pt 2): R1541–R1544.

201 Kjems LL, Holst JJ, Volund A, Madsbad S. The influence of GLP-1 on glucose-stimulated insulin secretion: effects on beta-cell sensitivity in type 2 and nondiabetic subjects. Diabetes 2003; 52: 380–386.

202 Chang AM, Jakobsen G, Sturis J, Smith MJ, Bloem CJ, An B et al. The GLP-1 derivative NN2211 restores beta-cell sensitivity to glucose in type 2 diabetic patients after a single dose. Diabetes 2003; 52: 1786–1791.

203 Egan JM, Meeney GS, Habener JF, Elahi D. Glucagon-like peptide-1 augments insulin-mediated glucose uptake in the obese state. J Clin Endocrinol Metab 2002; 87: 3768–3773.
225 Austin C, Lo G, Nandha KA, Meleagros L, Bloom SR. Cloning and characterization of the CDNA encoding the human neuromedin U (NmU) precursor: NmU expression in the human gastrointestinal tract. J Mol Endocrinol 1995; 14: 157–169.

226 Austin C, Oka M, Nandha KA, Legon S, Khandan-Nia N, Lo G et al. Distribution and developmental pattern of neuromedin U expression in the rat gastrointestinal tract. J Mol Endocrinol 1994; 12: 257–263.

227 Augood SJ, Keast JR, Emerson PC. Distribution and characterisation of neuromedin U-like immunoreactivity in rat brain and intestine and in guinea pig intestine. Regul Pept 1988; 20: 281–292.

228 Ballesta J, Carlei F, Bishop AE, Steel JH, Gibson SJ, Fahey M et al. Distribution and characterisation of Pancreatic gastrin stimulates islet differentiation of transforming growth exocrine pancreas tissue. and increases islet mass from transdifferentiated but not from normal pancreas. Islets. 2009; 212: 138–143.

229 Honzawa M, Sudo T, Minamino N, Kangawa K, Matsuo H. Neuromedin U-like immunoreactivity in rat intestine: regional distribution and immunohistochemical study. Neuropeptides 1990; 15: 1–9.

230 Kaczmarek P, Malendowicz LK, Pruszyńska-Oszmala E, Wojciechowicz T, Szczepankiewicz D, Szudelski T et al. Neuromedin U receptor 1 expression in the rat endocrine pancreas and evidence suggesting neuromedin U suppressive effect on insulin secretion from isolated rat pancreatic islets. Int J Mol Med 2006; 18: 951–955.

231 Alfa RW, Park S, Skelly KR, Poffenberger G, Jain N, Gu X et al. Suppression of insulin production and secretion by a decretin hormone. Cell Metab 2015; 21: 323–333.

232 Kaczmarek P, Malendowicz LK, Fabis M, Ziółkowska A, Pruszyńska-Oszmala E, Sassek M et al. Does somatostatin confer insulinostatic effects of neuromedin u in the rat pancreas? Pancreas 2009; 38: 208–212.

233 Wang TC, Bonner-Weir S, Oates PS, Chulak M, Simon B, Merlino GT et al. Pancreatic gastrin stimulates islet differentiation of transforming growth factor alpha-induced ductular precursor cells. J Clin Invest 1993; 92: 1349–1356.

234 Rooman I, Lardon J, Bouwens L. Gastrin stimulates beta-cell neogenesis and increases islet mass from transdifferentiated but not from normal exocrine pancreas tissue. Diabetes 2002; 51: 686–690.

235 Leung-Theung-Long S, Carlei F, Bishop AE, Steel JH, Gibson SJ, Fahey M et al. Distribution and characterisation of Pancreatic gastrin stimulates islet differentiation of transforming growth exocrine pancreas tissue. and increases islet mass from transdifferentiated but not from normal pancreas. Islets. 2009; 212: 138–143.

236 Ahren B, Pettersson M, Uvnäs-Moberg K, Gutniak M, Efendic S. Effects of Pancreatic gastrin stimulates islet differentiation of transforming growth exocrine pancreas tissue. and increases islet mass from transdifferentiated but not from normal pancreas. Islets. 2009; 212: 138–143.

237 Simon MC, Strassburger K, Nowotny B, Kolb H, Nowotny P, Burkart V et al. Intake of Lactobacillus reuteri improves incretin and insulin secretion in glucose-tolerant humans: a proof of concept. Diabetes Care 2015; 38: 1827–1834.

238 Larsen N, Vegosen FK, van den Berg FW, Nielsen DS, Andreassen AS, Pedersen BK et al. Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. Plos ONE 2010; 5: e9085.

239 Moreno-Indias I, Cardona F, Tinhafones FJ, Queipo-Ortuno MI. Impact of the gut microbiota on the development of obesity and type 2 diabetes mellitus. Front Microbiol 2014; 5: 190.

240 Huang I, Park YJ, Kim YR, Kim YN, Ka S, Lee HY et al. Alteration of gut microbiota by vancomycin and bacitracin improves insulin resistance via glucagon-like peptide 1 in diet-induced obesity. FASEB J 2015; 29: 2397–2411.

241 Simon MC, Strassburger K, Nowotny B, Bolb H, Nowotny P, Burkart V et al. Intake of Lactobacillus reuteri improves incretin and insulin secretion in glucose-tolerant humans: a proof of concept. Diabetes Care 2015; 38: 1827–1834.

242 Larsen N, Vegosen FK, van den Berg FW, Nielsen DS, Andreassen AS, Pedersen BK et al. Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. Plos ONE 2010; 5: e9085.

243 Moreno-Indias I, Cardona F, Tinhafones FJ, Queipo-Ortuno MI. Impact of the gut microbiota on the development of obesity and type 2 diabetes mellitus. Front Microbiol 2014; 5: 190.

244 Larsen N, Vegosen FK, van den Berg FW, Nielsen DS, Andreassen AS, Pedersen BK et al. Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. Plos ONE 2010; 5: e9085.
Pancreatic regulation of glucose homeostasis
PV Röder et al.

269 Yamauchi T, Kamon J, Minokoshi Y, Ito Y, Waki H, Uchida S et al. Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. Nat Med 2002; 8: 1288–1295.

270 Wijesekara N, Krishnamurthy M, Bhattacharjee A, Suhail A, Sweeney G, Wheeler MB. Adiponectin-induced ERK and Akt phosphorylation protects against pancreatic beta cell apoptosis and increases insulin gene expression and secretion. J Biol Chem 2010; 285: 33623–33631.

271 Gu W, Li X, Cui Y, Ye L, Tang J et al. Global adiponectin augments insulin secretion from pancreatic islet beta cells at high glucose concentrations. Endocrine 2006; 30: 217–221.

272 Boucher J, Masri B, Daviaud D, Gesta S, Guigne C, Mazzucotelli A et al. Apelin, a newly identified adipokine up-regulated by insulin and obesity. Endocrinology 2005; 146: 1764–1771.

273 Wei L, Hou X, Tatome M. Regulation of apelin mRNA expression by insulin and glucocorticoids in mouse 3T3-L1 adipocytes. Regul Pept 2005; 132: 27–32.

274 Takahashi M, Okimura Y, Iguchi G, Nishizawa H, Yamamoto M, Suda K et al. Chemerin regulates beta-cell function in mice. Sci Rep 2011; 1: 123.

275 Takahashi M, Takahashi Y, Takahashi K, Zolotaryov FN, Hong KS, Sell H, Laurencikiene J, Taube A, Eckardt K, Cramer A, Horrighs A, Meinert CL, Knatterud GL, Prout TE, Klimt CR. A study of the effects of omentin as a novel depot-specific adipokine in human primary skeletal muscle cells. Diabetes 2009; 58: 2731–2740.

276 Tan BK, Adya R, Farhatullah S, Lewandowski KC, O’Hare P, Lennert H et al. Omentin: a novel adipokine, is increased in overweight insulin-resistant women with polycystic ovary syndrome: ex vivo and in vivo regulation of omentin-1 by insulin and glucose. Diabetes 2008; 57: 801–808.

277 Aiken G, Vinsloy A, Salazar G, Bataille D, Blache P. Characterization of low-affinity binding sites for glimepiride on the Kir6.2 subunit of the beta-cell ATP-sensitive K+ channel. Biochim Biophys Acta 2009; 1792: 707–712.

278 Schwartz TB, Meinert CL. The UGDP controversy: thirty-four years of contentious ambiguity laid to rest. Perspect Biol Med 2004; 47: 564–574.

279 Babenko AP, Gonzalez G, Bryan J. The tolbutamide site of SUR1 and a mechanism for its functional coupling to K(ATP) channel closure. FEBS Lett 1999; 459: 367–376.

280 Koster JC, Sha Q, Nichols CG. Sulfonfonyurea and K(+)-channel opener sensitivity of K(ATP) channels. Functional coupling of Kir6.2 and SUR1 subunits. J Gen Physiol 1999; 114: 203–213.

281 Meinert CL, Klimt CR. The tolbutamide site of SUR1 and the ATP-sensitive K+ channel in insulin-secreting pancreatic beta-cells. J Mol Endocrinol 1999; 22: 113–123.

282 Gloyn AL, Weedon MN, Owen KR, Turner MJ, Knight BA, Hitman G et al. Large-scale association studies of variants in genes encoding the pancreatic beta-cell KATP channel subunits Kir6.2 (KCNJ11) and SUR1 (Abcc8) confirm that the KCNJ11 E23K variant is associated with type 2 diabetes. Diabetes 2003; 52: 568–572.

283 FGF21 expression is an Akt-regulated myokine. Diabetes 2003; 52: 568–572.

284 Ribas F, Villarroya J, Kitazawa R et al. Chemerin regulates beta-cell function in mice. Sci Rep 2011; 1: 123.

285 Takahashi M, Okimura Y, Iguchi G, Nishizawa H, Yamamoto M, Suda K et al. Chemerin regulates beta-cell function in mice. Sci Rep 2011; 1: 123.

286 Meitner CL, Knatterud GL, Prout TE, Klimt CR. A study of the effects of omentin as a novel depot-specific adipokine in human primary skeletal muscle cells. Diabetes 2009; 58: 2731–2740.

287 Tan BK, Adya R, Farhatullah S, Lewandowski KC, O’Hare P, Lennert H et al. Omentin: a novel adipokine, is increased in overweight insulin-resistant women with polycystic ovary syndrome: ex vivo and in vivo regulation of omentin-1 by insulin and glucose. Diabetes 2008; 57: 801–808.

288 Yang RZ, Lee MJ, Hu H, Pray J, Wu HB, Hansen BC et al. Apolin, a newly identified adipokine up-regulated by insulin and obesity. Endocrinology 2005; 146: 1764–1771.

289 Yamauchi T, Kamon J, Minokoshi Y, Ito Y, Waki H, Uchida S et al. Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. Nat Med 2002; 8: 1288–1295.
353 Neuschwander-Tetri BA, Isley WL, Oki JC, Ramrakhiani S, Quaison SG, Phillips NJ et al. Troglitazone-induced hepatic failure leading to liver transplantation. A case report. Ann Intern Med 1998; 129: 38–41.

354 Kohroser J, Mathai J, Reichfeld J, Banner BF, Bonkovsky HL. Hepatotoxicity due to troglitazone: report of two cases and review of adverse events reported to the United States Food and Drug Administration. Am J Gastroenterol 2000; 95: 272–276.

355 Niessen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007; 356: 2457–2471.

356 Berger J, Bailey P, Biswas C, Cullinan CA, Doebber TW, Hayes NS et al. Thiazolidinediones produce a conformational change in periloxosomal proliferator-activated receptor-gamma: binding and activation correlate with antidiabetic actions in db/db mice. Endocrinology 1996; 137: 4189–4195.

357 Schoonjans K, Peinado-Onsurbe J, Lefebvre AM, Heyman RA, Briggs M, Deeb S et al. PPARalpha and PPARgamma activators direct a distinct tissue-specific transcriptional response via a PPRE in the lipoprotein lipase gene. EMBO J 1996; 15: 5336–5348.

358 Dumasia R, Eagle KA, Kline-Rogers E, May N, Cho L, Mukherjee D. Role of PPAR- gamma agonist thiazolidinediones in treatment of pre-diabetic and diabetic individuals: a cardiovascular perspective. Curr Drug Targets Cardiovasc Haematol Disord 2005; 5: 377–386.

359 Smith SR, De Jonge L, Volaufova J, Li Y, Xie H, Bray GA. Effect of pioglitazone on body composition and energy expenditure: a randomized controlled trial. Metabolism 2005; 54: 24–32.

360 Ishida M, Takizawa M, Ozawa S, Nakamura Y, Yamaguchi S, Katsuda H et al. Pioglitazone improves insulin secretory capacity and prevents the loss of beta-cell mass in obese diabetic db/db mice: Possible protection of beta cells from oxidative stress. Metabolism 2004; 53: 488–494.

361 Dianl AR, Sawada G, Wyse B, Murray FT, Kham P. Pioglitazone preserves pancreatic islet structure and insulin secretory function in three murine models of type 2 diabetes. Am J Physiol Endocrinol Metab 2004; 286: E116–E122.

362 Kawasaki F, Matsuda M, Kanda Y, Inoue H, Kaku K. Structural and functional analysis of pancreatic islets preserved by pioglitazone in db/db mice. Am J Physiol Endocrinol Metab 2005; 288: E510–E518.

363 Kimura T, Kaneto H, Shimoda M, Hirakura H, Okauchi S, Kohara K et al. Protective effects of pioglitazone and/or iraglutide on pancreatic beta-cells in db/db mice: comparison of their effects between in an early and advanced stage of diabetes. Mol Cell Endocrinol 2015; 400: 78–89.

364 Kanda Y, Shimoda M, Haramotome S, Tawaramoto K, Kawasaki F, Hashiramoto M et al. Molecular mechanism by which pioglitazone preserves pancreatic beta-cells in obese diabetic mice: evidence for acute and chronic actions as a PPARgamma agonist. Am J Physiol Endocrinol Metab 2010; 298: E278–E286.

365 Wachtler-Hagedoorn RE, Priebe MG, Heimweg JA, Heiner AM, Elzinga H, Wachters-Hagedoorn RE et al. Acarbose treatment and the risk of cardiovascular disease and hypertensive subjects with and without prior myocardial infarction. N Engl J Med 2003; 349: 204–210.

366 Troglitazone-induced hepatic failure leading to liver transplantation. A case report. Ann Intern Med 1998; 129: 38–41.

367 Chiasson JL, Josse RG, Gornis R, Hanefeld M, Karakis A, Laakso M. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. JAMA 2003; 290: 486–494.

368 Goda T, Suruga K, Komori A, Kuranuki S, Mochizuki K, Makita Y et al. Effects of miglitol, an alpha-glucosidase inhibitor, on glycemic status and histopathological changes in islets in non-obese, non-insulin-dependent diabetic Goto-Kakizaki rats. Br J Nutr 2007; 98: 702–710.

369 Koyama M, Wada R, Mizukami H, Sakuraba H, Oka H, Ikeda H et al. Inhibition of progressive reduction of islet beta-cell mass in spontaneously diabetic Goto-Kakizaki rats by alpha-glucosidase inhibitor. Metabolism 2000; 49: 347–352.

370 Fukaya N, Mochizuki K, Tanaka Y, Kuramata T, Juin Z, Fuchimori M et al. The alpha-glucosidase inhibitor miglitol delays the development of diabetes and dysfunctional insulin secretion in pancreatic beta-cells in OLETF rats. Eur J Pharmacol 2009; 624: 51–57.

371 Hanefeld M, Spacher F. Acarbose: oral anti-diabetes drug with additional cardiovascular benefits. Expert Rev Cardiovasc Ther 2008; 6: 53–63.

372 Huisman MA, Daniel PB, Habener JF. Glucagon stimulates expression of the inducible cAMP early repressor and suppresses insulin gene expression in pancreatic beta-cells. Diabetes 2000; 49: 1681–1690.

373 Greenbaum CJ, Havel PJ, Taborsky GJ Jr, Klaff L. Intra-islet insulin permits glucose to directly suppress pancreatic A cell function. J Clin Invest 1991; 88: 767–773.

374 Xu E, Kumar M, Yang Z, Ju W, Obata T, Zhang N et al. Intra-islet insulin suppresses glucagon secretion. Biochem Biophys Res Commun 2005; 332: 47–52.

375 Meier J, Kjems LL, Veldhuis JD, Lefebvre P, Butler PC. Postprandial suppression of glucagon secretion depends on intact pulsatile insulin secretion: further evidence for the intraislet insulin hypothesis. Diabetes 2006; 55: 1051–1056.

376 Duncan BB, Schmidt MI, Pankow JS, Ballantyne CM, Couper D, Vigo A et al. Low-grade systemic inflammation and the development of type 2 diabetes: the atherosclerosis risk in communities study. Diabetes 2003; 52: 1799–1805.

377 de Jager J, Dekker JM, Kooy A, Kostense PJ, Nijpels G, Heine RJ et al. Endothelial dysfunction and low-grade inflammation explain much of the excess cardiovascular mortality in individuals with type 2 diabetes: the Hoon Study. Arterioscler Thromb Vasc Biol 2006; 26: 1086–1093.

378 Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998; 339: 229–234.

379 Vainio T, Scharling H, Jensen JS, Vestergaard H. The independent effect of type 2 diabetes mellitus on ischemic heart disease, stroke, and death: a population-based study of 13,000 men and women with 20 years of follow-up. Arch Intern Med 2004; 164: 1422–1426.

380 Adler AI, Stevens RJ, Manley SE, Bilous RW, Cull CA, Holman RR. Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). Kidney Int 2003; 63: 225–232.

381 Ravik M, Brosh D, Ravid-Safran D, Levy Z, Rachmani R. Main risk factors for nephropathy in type 2 diabetes mellitus are plasma cholesterol levels, mean blood pressure, and hyperglycemia. Arch Intern Med 1998; 158: 998–1004.

382 Morawski G, Yamamoto T, Shibutani Y, Aoki E, Tsuchumi Z, Takahashi S et al. Elevated levels of interleukin-18 and tumor necrosis factor-alpha in serum of patients with type 2 diabetes mellitus: relationship with diabetic nephropathy. Metabolism 2003; 52: 605–608.

383 Wannamethee SG, Lowe GD, Rumley A, Cherry L, Whincup PH, Sattar N. Adipokines and risk of type 2 diabetes in older men. Diabetes Care 2007; 30: 1200–1205.

384 Milewicz A, Mikulski E, Bidzinska B, Plasma insulin, cholecystokinin, gallamine, neurotideptide and leptin levels in obese women with and without type 2 diabetes mellitus. Int J Obes Relat Metab Disord 2000; 24 Suppl 2: S152–S153.

385 Katsuki A, Uraoka H, Gabaazza EC, Murashima S, Nakatani K, Tagoshi K et al. Circulating levels of active ghrilin is associated with abdominal adiposity, hyperinsulinemia and insulin resistance in patients with type 2 diabetes mellitus. Eur J Endocrinol 2004; 151: 573–577.

386 Poykko SM, Kelloskki E, Horkkio S, Kauma H, Kesaniemi YA, Ukkola O. Low plasma ghrilin is associated with insulin resistance, hypertension, and the prevalence of type 2 diabetes. Diabetes 2003; 52: 2546–2553.
393 Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 2001; 344: 1343–1350.

394 Lim EL, Hollingsworth KG, Aribisala BS, Chen MJ, Mathers JC, Taylor R. Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. *Diabetologia* 2011; 54: 2506–2514.

395 Gustavsson N, Lao Y, Maximov A, Chuang JC, Kostromina E, Repa JJ et al. Impaired insulin secretion and glucose intolerance in synaptotagmin-7 null mutant mice. *Proc Natl Acad Sci USA* 2008; 105: 3992–3997.

396 Shu Y, Liu X, Yang Y, Takahashi M, Gilis KD. Phosphorylation of SNAP-25 at Ser187 mediates enhancement of exocytosis by a phorbol ester in INS-1 cells. *J Neurosci* 2008; 28: 21–30.

397 Lilja L, Johansson JU, Gromada J, Mandic SA, Fried G, Berggren PO et al. Cyclin-dependent kinase 5 associated with p39 promotes Munc18-1 phosphorylation and Ca(2+)-dependent exocytosis. *J Biol Chem* 2004; 279: 29534–29541.

398 Dixit SS, Wang T, Manzano EJ, Yoo S, Lee J, Chiang DY et al. Effects of CaMKII-mediated phosphorylation of ryanodine receptor type 2 on islet calcium handling, insulin secretion, and glucose tolerance. *PLoS ONE* 2013; 8: e58655.

399 Dzhura I, Chepurny OG, Leech CA, Roe MW, Dzhura E, Xu X et al. Phospholipase C-epsilon links Epac2 activation to the potentiation of glucose-stimulated insulin secretion from mouse islets of Langerhans. *Islets* 2011; 3: 121–128.

400 Kang L, He Z, Xu P, Fan J, Betz A, Brose N et al. Munc13-1 is required for the sustained release of insulin from pancreatic beta cells. *Cell Metab* 2006; 3: 463–468.

401 Kwan EP, Xie L, Sheu L, Nolan CJ, Prentki M, Betz A et al. Munc13-1 deficiency reduces insulin secretion and causes abnormal glucose tolerance. *Diabetes* 2006; 55: 1421–1429.

402 Yaekura K, Julyan R, Wicksteed BL, Hays LB, Alarcon C, Sommers S et al. Insulin secretory deficiency and glucose intolerance in Rab3A null mice. *J Biol Chem* 2003; 278: 9715–9721.

403 Torii S, Takeuchi T, Nagamatsu S, Izumi T. Rab27 effector granuphilin promotes the plasma membrane targeting of insulin granules via interaction with syntaxin 1a. *J Biol Chem* 2004; 279: 22532–22538.

404 Betts GJ, Desaix P, Johnson E, Korol O, Kruse D, Poe B et al. *Human Anatomy and Physiology*. OpenStax College: Houston, TX, USA, 2013.

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