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Modulation of Pancreatic Exocrine and Endocrine Secretion

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Abstract

Purpose of review—Recent advances in the regulation of pancreatic secretion by secretagogues, modulatory proteins and neural pathways are discussed.

Recent findings—Downstream events involved in secretagogue-stimulation of pancreatic secretion have been have been elucidated through characterization of the Src kinase pathway. An additional mechanism regulating vagus nerve effects on the pancreas involves Group II and III metabotropic glutamate receptors that are located presynaptically on certain vagal pancreas-projecting neurons. Hypothalamic neurons perceive glucose and regulate insulin release by direct communication with islets, and activation of POMC neurons by leptin enhances insulin secretion and modulates glucose but not energy homeostasis. Ghrelin and somatostatin mediate glucose-stimulated insulin secretion by differential receptor signaling that is dependent on the amount of ghrelin and state of receptor heterodimerization. Endoplasmic reticulum (ER) stress and loss-of-function mutations of a key ER stress protein are associated with disruption of membrane translocation and reduction in insulin secretion. The importance of hormones, neuropeptides, amino acids, cytokines and regulatory proteins in pancreatic secretion and the pathophysiology of type 2 diabetes are also discussed.

Summary—The biomolecular pathways regulating pancreatic secretions are still not fully understood. New secretagogues and mechanisms continue to be identified and this information will aid in drug discovery and development of new and improved therapy for pancreatic disorders.

Keywords

pancreas; endocrine; exocrine; secretion; insulin

Introduction

The exocrine and endocrine functions of the pancreas are performed by acinar and endocrine cell populations, respectively. Acinar cells are organized in clusters and upon stimulation, discharge digestive enzymes into a system of intercalated ducts which empty into the proximal duodenum. Inflammation produces acute or chronic pancreatitis and may result in loss of acinar function. Hormones such as glucagon, insulin and somatostatin are secreted into the blood by α-, β- and δ-cells of the islets of Langerhans, and mediate pancreatic

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endocrine function. These hormones impact various target organs such as the liver to facilitate glucose homeostasis. Numerous hormones and the central and peripheral nervous systems regulate pancreatic secretion through cellular receptors and their signal transduction cascades. Locally, paracrine and autocrine pathways exert secretory control. This review places into context information published in the field of pancreatic secretion within the past year.

Regulation of Exocrine Secretion

Pancreatic exocrine secretion is mediated by various secretagogues and regulated by intracellular signaling pathways.

Peptide regulation of acinar secretion

TLQP-21 is a bioactive peptide derived from VGF neuropeptide. It is expressed in pancreatic islets as well as in autonomic nerves innervating the pancreas. Incubation of pancreatic lobules with TLQP-21 resulted in dose-dependent amylase release, which was blocked by inhibitors of prostaglandin synthesis but was unaffected by the muscarinic antagonist atropine [1*]. Although the mechanism of amylase release by TLPQ-21 has not yet been elucidated, there is preliminary evidence to suggest that intracellular Ca^{2+} signaling may be involved [2*]. This study provides evidence that VGF-like peptides may directly affect acinar secretion and supports the concept that islet hormones and transmitters regulate pancreatic acinar function.

Src kinase mediates secretagogue activation of acinar cells

The Src family of kinases plays important roles in many cellular processes including secretion and growth. In acinar cells, Src kinases are involved with enzyme secretion, membrane recycling, protein synthesis and regulating intracellular calcium levels. Activation of rat acini by CCK caused rapid and sustained phosphorylation of the Src kinase Yes [3*]. Other secretagogues that elicited phospholipase C-mediated augmentation of intracellular Ca^{2+} and stimulation of protein kinase C (PKC) also activated Yes indicating that this kinase plays a central role in secretagogue stimulation of acinar cells. Phosphorylated Yes interacted with other cellular kinases involved in numerous signaling cascades, including PKCδ which activates NF-κB, a protein that plays a critical role in the development of acute pancreatitis [4]. *Yes* mRNA was differentially upregulated under conditions of trypsinogen activation in AR42J cells [5*]. These studies provide evidence that Src kinases are key regulators of acinar cell function and make Yes an attractive therapeutic target for drug development.

Neuronal Regulation of Pancreatic Secretion

The pancreas is extensively innervated and secretion is modulated by neurotransmitter release.

Vagal innervation of exocrine and endocrine pancreas

Pancreatic secretion is regulated in part by neuronal projections from the dorsal motor (DMV) nucleus of the vagus, located in the brain stem. Moreover, separate populations of

vagal neurons appear to regulate endocrine and exocrine secretion. Group II and III metabotropic glutamate receptors (G protein-coupled receptors (GPCRs) coupled to primarily to $G_{i/o}$) were located on excitatory and inhibitory pre-synaptic terminals of pancreas-projecting DMV neurons [6*]. Neurons responsive to group II metabotropic glutamate receptor agonists were activated by CCK and pancreatic polypeptide and had the ability to regulate exocrine secretion. Some group II and III metabotropic glutamate receptor-responsive neurons were stimulated by exendin-4 [a glucagon-like peptide-1 (GLP-1) analog] and regulated insulin secretion. These studies showed that in addition to γ-amino butyric acid, the neurotransmitter glutamate can also modulate pancreatic exocrine and endocrine secretion through distinct vagal neurons.

Hypothalamic signaling and islet secretion

The hypothalamus also plays an important role in glucose-stimulated insulin release GSIS [7*]. Administration of glucose into the third ventricle 30 minutes prior to an intravenous glucose tolerance test enhanced insulin secretion accompanied with a rapid decline in blood glucose. Infusion of glucokinase inhibitors, which blocked glucose metabolism, decreased GSIS and worsened glucose tolerance. The mechanisms by which hypothalamic signaling and islet hormone release are integrated remain to be unraveled.

Hormonal Regulation of Endocrine Secretion

Many hormones regulate pancreatic endocrine secretion by interacting with cells in the islets of Langerhans.

Incretin effects in diabetes

The incretins, GLP-1 and glucose-dependent insulinotropic polypeptide, are secreted by intestinal L and K cells, respectively, and stimulate postprandial insulin release. In a double-blind, randomized trial, the effect of incretins on both phases of insulin secretion, in healthy individuals and patients with type 2 diabetes were compared [8*]. Using hyperglycemic clamp, approximately 60% of insulin released after a duodenal meal infusion was due to incretins, primarily GLP-1. While the effect of incretins on phase two insulin secretion did not differ significantly between healthy adults and diabetic patients, incretins greatly enhanced phase one insulin secretion in diabetics. Incretins also suppressed glucagon secretion in both groups. These studies demonstrated that the effect of incretins on β-cells is not impaired in type 2 diabetes but decreased insulin secretion is perhaps due to reduced β-cell mass or other factors such as neuronal dysfunction.

Ghrelin and somatostatin receptor interactions regulate insulin release

Ghrelin is a 28 amino acid orexigenic hormone released by gastric endocrine cells under fasting condition. In isolated rat islets, ghrelin counteracted the insulinotropic effects of GLP-1-mediated GSIS by preventing elevation of intracellular Ca^{2+} and cAMP levels [9*]. Ghrelin also regulated the effect of somatostatin on GSIS. Under conditions of low glucose, ghrelin was elevated concomitant with a reduction in somatostatin [10**]. The ghrelin receptor (growth hormone secretagogue receptor type 1a (GHS-R1a)) dimerized with somatostatin receptor, subtype 5 (SSTR5) located on β-cells. This heterodimer coupled with

inhibitory G proteins suppressed cAMP signaling, and consequently GSIS. When glucose levels increased (and ghrelin levels decreased), somatostatin was elevated. Binding of somatostatin to SSTR5 led to disruption of the heteromer, signaling of GHS-R1a through $G_{\alpha q11}$, and a rise in cAMP and GSIS. The role of ghrelin in GSIS through its interactions with other hormones highlights an unexpected and complex aspect of pancreatic endocrine regulation.

Leptin and glucose homeostasis

Leptin is secreted by adipocytes and plays a significant role in glucose homeostasis [11]. Mice carrying a point mutation in the leptin receptor (LEPR) gene (db/db) are obese, have high plasma insulin levels and impaired glucose tolerance. LEPRs are expressed in many areas of the brain. The contribution of LEPR (long isoform) expressed in hypothalamic proopiomelanocortin (POMC) neurons on glucose homeostasis, was evaluated in mice with LEPR expression limited to POMC neurons [12**]. Global deletion of LEPR caused obesity and hyperglycemia, whereas specific expression of LEPR in POMC neurons completely restored glucose levels and improved insulin sensitivity, suggesting that LEPR signaling in POMC neurons is sufficient to modulate glucose homeostasis. These results revealed a dichotomy in leptin signaling: LEPR in POMC neurons regulated glucose homeostasis but did not modulate appetite and suppression of food intake.

Independent of leptin's regulatory effects on glucose homeostasis (discussed above), it interacted directly with receptors located on pancreatic β-cells to attenuate insulin gene expression and secretion. Analysis of leptin, GLP-1, and glybenclamide interaction in regulation of insulin secretion in pancreas-specific LEPR knockout mice showed that leptin inhibited insulin secretion by K_{ATP} channel-dependent and independent pathways [13]. Sulfonylurea derivatives interacted with the SUR subunit of K_{ATP} channels and induced channel closure, leading to elevated intracellular Ca^{2+} and release of insulin. GLP-1 and sulfonylureas enhanced insulin release in LEPR knockout mice, suggesting that removal of leptin suppression of GSIS could provide a therapeutic tool in the treatment of type 2 diabetes.

TLQP-21 Stimulates Insulin Secretion

TLQP-21 augmented insulin release from human and rat islets in the presence of high concentrations of glucose [14**]. Similarly, administration of TLQP-21 in fasted rats did not cause insulin secretion but TLQP-21 injection after an initial bolus of glucose, enhanced plasma insulin concomitant with a decrease in peak glucose, suggesting that TLQP-21 potentiates GSIS *in vivo*. Treatment of Zucker diabetic rats with TLQP-21 decreased fed glucose levels, delayed onset of type 2 diabetes, and increased β-cell mass, showing that this peptide has therapeutic potential in the treatment of type 2 diabetes.

Inhibition of insulin release by galanin

Galanin is a small neuropeptide that is widely distributed in the nervous system and performs diverse physiological functions. It is expressed in autonomic nerve terminals of the endocrine pancreas and serves as a negative regulator of insulin secretion. Galanin GPCRs and five members of pertussis toxin-sensitive G proteins are expressed in pancreatic islets

[15*]. Galanin failed to potentiate K_{ATP} channels, block Ca^{2+} current, or raise blood glucose levels in $G_o2\alpha$ knockout mice, indicating that this G protein plays a key role in regulating galanin-mediated insulin release.

Melatonin inhibits insulin release

Melatonin is synthesized by the pineal gland and maintains circadian rhythm. Melatonin receptors, MT_1 and MT_2, are expressed in pancreatic islets and mutations in these receptors have been associated with elevated glucose levels. Melatonin action on MT_2 has previously been shown to diminish insulin secretion by reducing second messenger signaling. Using a combination of shRNA interference and knockout mouse models, it was demonstrated that melatonin also acts on MT_1 to decrease intracellular cAMP and insulin secretion [16]. Knockdown of MT_1 in INS-1 β-cells caused significant de-repression of insulin gene expression and basal insulin secretion. In addition, the modulatory role of melatonin on GLP-1 mediated insulin secretion was dependent of the expression of MT_1 receptors. Thus both MT_1 and MT_2 receptors independently or in conjunction can play a role in insulin secretion.

Non-hormonal Mediators of Endocrine Secretion

Pancreatic endocrine secretion is also mediated by non-hormonal secretagogues and cellular signaling proteins.

ER stress and β-cell dysfunction

Accumulating evidence suggests that endoplasmic reticulum (ER) stress contributes to β-cell dysfunction and may be important for the development of type 2 diabetes. Wolfram syndrome 1 (WFS1) is an endoplasmic reticulum (ER) stress response protein that is expressed in β-cells as well as other tissues [17, 18]. Overexpression of WFS1 in primary rat islets increased insulin gene expression, cellular insulin content, and GSIS by a mechanism independent of ER stress level [19**]. Using knockout and mutant mice, as well as lentiviral-mediated WFS1 overexpression, the authors showed that WSF1 is critical for β-cell function and insulin release through cAMP stimulated pathways. *Wsf1*$^{-/-}$ islets did not produce cAMP or secrete insulin in response to glucose and incretins. When cells are stimulated by glucose (in the absence of ER stress), WFS1 translocated from the ER to the plasma membrane and formed a complex with adenylyl cyclase 8 and calmodulin, stimulating cAMP generation, insulin biosynthesis and secretion. The reduction of WFS1 on the plasma membrane during ER stress may contribute to β-cell dysfunction and diabetes.

Amino acid supplementation enhances insulin secretion

Protein restriction can negatively affect glucose regulation. A recent study demonstrated that doubling the amount of leucine in high fat diet-fed mice improved glucose tolerance and insulin secretion [20]. Leucine augmented insulin secretion through down-regulation of the adrenergic α_{2A} receptor by activating mTOR (a serine threonine kinase belonging to the phosphoinositol-3-kinase family). Inhibition of mTOR by rapamycin and activation of α_2 adrenergic receptors by clonidine, suppressed leucine stimulated insulin release whereas antagonists of α_2 adrenergic receptors increased insulin secretion [21**]. These biochemical

findings appear to have clinical relevance since it was observed in a retrospective analysis that renal transplant patients who received a combination of rapamycin and clonidine had a higher incidence of new onset of diabetes after transplantation.

Apolipoprotein A-IV enhances insulin secretion

Ingestion of lipids leads to the synthesis and secretion of apolipoprotein A-IV (apoA-IV) by enterocytes. It circulates as free protein or in association with HDL and exogenous apoA-IV administration reduced food intake [22]. ApoA-IV levels increased after gastric bypass surgery, coincident with amelioration of diabetes. Previous studies have suggested that apoA-I and apoA-II either alone or in association with HDL increased insulin mRNA expression and secretion in a glucose-dependent manner, by activation of K_{ATP} channels and elevation of intracellular Ca^{2+} [23]. ApoA-IV similarly increased glucose-dependent insulin secretion and this effect was inhibited by K_{ATP} and Ca^{2+} channel blockers [24**]. ApoA-IV knockout mice have delayed glucose clearance and reduced insulin secretion, which is exacerbated by a high fat diet. Administration of apoA-IV in knockout or diabetic KKAy mice significantly improved glucose levels and insulin secretion. Since apolipoproteins are not expressed in the pancreas, it will be interesting to identify the membrane receptors that bind apolipoproteins and activate insulin secretion.

Interleukin-6 promotes insulin secretion

It was recently demonstrated that exercise-induced release of cytokine IL-6 from muscles stimulated GLP-1 release, which promoted insulin secretion, causing a reduction in circulating glucose [25]. IL-6 can also act directly on BRIN-BD11 β-cells and mouse islets to stimulate insulin release in a dose- and time-dependent manner [26*]. This effect was accompanied with an increase in phosphorylated AMP-activated protein kinase (AMPK), which plays a key role in energy homeostasis and is a known mediator of IL-6 action in the skeletal muscle [27]. CAMKK, an upstream regulator of AMPK was also elevated. In BRIN-BD11 β-cells, expression of iNOS was greatly enhanced suggesting that IL-6 could potentially regulate insulin secretion through a NO-mediated signaling pathway.

Down-stream targets of GLP-1R activation alter insulin secretion

Small ubiquitin-related modifier (SUMO) proteins are found in many types of cells and modify protein function by reversible attachment or detachment. Exposure of mouse islets to high glucose was found to augment expression of SUMO isoforms [28*] which covalently modified GLP-1 receptor, diminished its trafficking to the membrane, and reduced insulin secretion. Recent studies have shown that SUMO can also modify glucokinase *in vitro* and modulate glucose metabolism [29]. It is anticipated that analysis of SUMO proteins in diabetic islets will help to elucidate the significance of this pathway in the dysregulation of insulin secretion.

Conclusion

In addition to the highlights covered in this review several other molecules including, preptin, apelin, obestatin, arginine and adenosine have been shown to influence insulin secretion. New insights into the regulation of pancreatic secretion by microRNAs suggest

that the function of these molecules merits further exploration and evaluation. The role of transcriptional factors such as Pax6 in hormone and receptor gene expression imposes additional levels of regulatory control and remain to be fully elucidated. Finally, genome-wide interaction mapping technologies are the latest trend in identification of gene networks that play important roles in multifactorial diseases such as type 2 diabetes.

Acknowledgments

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Key points

1. A VGF-derived peptide TLQP-21 plays an important in exocrine and endocrine secretion.
2. Leptin-responsive hypothalamic POMC neurons mediate glucose but not energy homeostasis.
3. Patients with type 2 diabetes have reduced GLP-1 mediated phase one insulin secretion and this effect was attributed to reduced β cell mass and/or neuronal signaling.
4. A unique mechanism of ghrelin and somatostatin signaling involves association of their receptors into heterodimers and regulation of insulin release.
5. Renal transplant patients treated with rapamycin or clonidine, have a higher incidence of new onset of diabetes after transplantation due to repression of insulin secretion.