

Regulation of Pancreatic Exocrine Function by Islet Hormones

M. Dolores Sans¹, Jason I.E. Bruce², and John A. Williams¹

¹Department of Molecular and Integrative Physiology, University of Michigan, Ann Arbor, MI ²Faculty of Biology, Medicine, and Health, School of Medical Sciences, University of Manchester, Manchester, UK

e-mail: mdsansg@umich.edu, jason.bruce@manchester.ac.uk, jawillms@umich.edu

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I. Introduction

The exocrine pancreas is regulated by nerves, mainly the vagus, and gastrointestinal hormones, especially cholecystokinin (CCK) and secretin. A third specific source of regulation is by peptide hormones from the Islets of Langerhans. Islet hormones are relevant because of structural relations within the pancreas. Except for some fishes which have a single larger collection of endocrine cells, islets are dispersed within the pancreas and have the ability to regulate exocrine cells both by local diffusion which manifests as peri-insular halos of acinar cells and by a specific vascular relationship, the islet-acinar portal system. The latter results in acinar cells being exposed to high concentrations of islet hormones and other regulatory molecules. Of these the best defined relationship is with insulin produced in islet beta cells which serves as a trophic factor for the exocrine pancreas, as a short-term signal promoting digestive enzyme synthesis at the translational level, and as part of a long-term control system where dietary carbohydrate leads to the synthesis of the carbohydrate targeted digestive enzyme, pancreatic amylase. Insulin also facilitates digestive enzyme secretion and regulates the membrane transport of glucose and

Ca²⁺. Earlier reviews of this topic include (12, 275, 330). Evidence for a direct effect of other islet peptides is less clear and some may exert an effect through regulating insulin secretion.

II. Structure and Vascular Supply of the Pancreas

A. Structure and distribution of Islets of the Pancreas

Pancreatic islets are collections of endocrine cells scattered through the exocrine pancreas making up 2-3% of the gland. Islets are made up of five types of endocrine cells known as α , β , δ , ϵ , and PP/F cells that synthesize and secrete, respectively, glucagon, insulin, somatostatin, ghrelin, and pancreatic polypeptide, all of which are considered peptide hormones. Beta cells are the most numerous cell type (60-70%) and form the core in rodent islets but are scattered throughout the human islet. Alpha cells make up about 20% and along with δ cells (1-2%) form a mantle on the outside of rodent islets. Some of the cell types are geographically distributed with PP/F cells primarily in the ventral lobe of the pancreas. By contrast, ϵ cells are developmentally regulated making up about 10% of the fetal islet but then differentiate

into α and β cells so that in the adult they are rare. Some of the endocrine cells also express a second biologically active peptide (12). Amylin and galanin are synthesized in β cells and are co-secreted with insulin. Pancreastatin is present in α , β , and δ cells where it is derived from chromogranin, and adrenomedulin is produced in PP/F cells. In understanding the effects of these islet peptides on the exocrine pancreas it is important to realize that some (insulin, glucagon and PP) are essentially unique to the islets but others like somatostatin are more broadly distributed in the GI tract, which could affect the exocrine pancreas locally or from systemic sources. Because islet peptides can regulate the other cells within the islet, effects of a particular peptide could be mediated directly on exocrine cells or indirectly by affecting the secretion of insulin or another islet peptide. Furthermore, some of these peptides can affect the CNS and vagal regulation of the exocrine pancreas. Receptors on exocrine pancreatic cells along with direct in vitro effects of islet peptides have been identified for insulin and somatostatin but not for glucagon or PP. Further details with references will be given in the sections on individual peptides.

B. Islet – acinar portal system

Blood flow to the pancreas has been reported to be 0.4 to 1.1 ml per g weight per min with most data from rats, rabbits, mice and dogs (288). Early studies injecting dye or ink into arteries feeding the pancreas showed rapid and intense perfusion of glomerular structures that were identified as Islets of Langerhans (68, 116, 198). Islet blood flow has been most often quantitated using microspheres. Such studies show that 5-20% of blood flow goes to the islets which have a relative blood flow 5-10 times higher than the exocrine pancreas (130, 177). The regulation of blood flow to the two portions of the pancreas is distinct with exocrine secretagogues such as CCK and VIP increasing blood flow to the exocrine pancreas (54, 129) and glucose increasing islet blood flow (131). In a study in rabbits, Lifson and colleagues concluded that essentially all blood flow to the islets goes

subsequently to the acinar capillaries (175). Considerable attention has also been paid to the pathway of capillaries within the islets as it pertains to which islet cells are upstream of the others (31, 183).

Early dye injection vascular perfusion studies also showed that small capillary vessels exited the islets and carried blood to the exocrine pancreas and these have been named the insulo – acinar portal system. This directional flow is facilitated by the fact that islet capillaries are slightly larger in diameter which should lead to higher capillary pressure (117, 314). In some species, there are also direct arterioles feeding the acinar tissue and venules draining the islets so not all islet effluent passes to the exocrine tissue. Similar results have been seen for rabbits, rats, mice, guinea pigs, cats, dogs and baboons (115). Evidence for the portal system also comes from scanning electron microscopy of vascular casts and from functional studies. Vascular casts are made by injecting resin or acrylate into the arteries and after polymerization the residual tissue is digested away leaving a three dimensional vascular cast which is coated with gold and viewed in a scanning electron microscope. Each islet has one or sometimes two afferent vessels which break down into a glomus-like capillary network. Efferent vessels similar in size to capillaries leave the islet and connect to the acinar capillaries (82, 83, 216, 225, 341). Similar findings have been made in the rat, rabbit, monkey, horse, baboon and human. Some controversy exists over the extent of this phenomenon especially in rats where Bonner-Weir reported that a large extent of islet blood was drained directly into venules (24) but this was subsequently disputed (204). Lifson and Lassa also described an acinar-ductal portal system in the rabbit pancreas (176). In any case, all blood from exocrine pancreas exits in venules which combine to form the pancreatic veins.

A different type of evidence for the islet-acinar portal system comes from physiological studies particularly using the perfused rat pancreas. Insulin added to the vascular perfusate enhances

the exocrine response to CCK and secretin (109, 137, 257, 258). Glucose, which by itself does not affect exocrine secretion, when added to the vascular perfusate enhances the release of insulin and potentiates exocrine secretion (89, 258). Other sugars that do not stimulate insulin secretion had no effect, and epinephrine, which blocks insulin secretion, blocked the potentiating effect of glucose. Since insulin can only come from the islets and would be carried away in the venous drainage in the single pass perfusion system, an effect on exocrine secretion can only come from endogenous insulin reaching exocrine cells by the portal system. Similar studies depleting endogenous somatostatin with cysteamine have also provided evidence for endogenous somatostatin acting through the portal system (238).

Based on the presence of the insulo-acinar portal system, an important question is what is the concentration of islet peptides in the exocrine interstitial compartment. Two estimates indicate that the concentration of insulin and somatostatin is in the nanomolar range. The first comes from a study evaluating saturable binding of iodinated tracer for insulin and somatostatin in the rat pancreas perfused anterograde or retrograde (219). Binding was higher for retrograde perfusion which was attributed to endogenous hormone released during anterograde perfusion. Displacement curves during retrograde perfusion indicated an interstitial concentration of insulin during anterograde perfusion with glucose of 7.5 nM and for somatostatin of 1.1 nM. A second study used a microdialysis technique which showed an unstimulated concentration of insulin of 0.4 nM during both retrograde and anterograde perfusion of dog pancreas (218). The response to stimulation with glucose plus arginine was markedly less during retrograde perfusion. Although the stimulated concentrations did not reach steady state, if insulin release went up 10 fold the interstitial exocrine concentration during glucose stimulation would be about 4 nM. Unfortunately, reported plasma insulin levels in fasting rats and dogs are quite variable with most

ranging from 50-400 pM. Much better data is available for humans where most fasting levels are reported to be 25-150 pM.

In summary, although the islet-acinar portal system does not account for all blood flow to exocrine pancreas cells, it does allow a significant fraction of exocrine acinar and duct cells to be exposed to higher concentrations of islet hormones than is the case for other organs. In addition, islet hormones can act directly on acinar cells via specific receptors or indirectly by affecting the release of other islet hormones.

III. Action of insulin on the exocrine pancreas

Insulin appears to be the most important of the classical islet hormones as a regulator of the exocrine pancreas and especially acinar cells. Evidence exists from both human studies and animal models and includes both physiology and disease. Experimental studies have been carried out at different levels of integration from the intact organism to cellular and molecular studies of acinar cells.

A. Clinical studies on the effects of diabetes on exocrine pancreas

For over one hundred years the pancreas of diabetic patients has been known to be smaller with increased fibrosis consistent with pathology of the entire pancreas and not just the islets (36). Diabetes is now divided into Type 1 or insulin dependent diabetes mellitus (IDDM) where destruction of beta cells leads to lack of insulin, Type 2 whose hallmark is insulin resistance and often does not require additional insulin, and most recently Type 3 which is due to exocrine pathology such as chronic pancreatitis. It has long been recognized that Type 1 and 2 patients may also suffer exocrine abnormalities ranging from subclinical to pancreatic exocrine insufficiency (PEI).

1. Loss of pancreatic mass in diabetes

Autopsy studies of Type 1 diabetes have shown decreased pancreatic weight and volume (91, 184). Methods have been developed to use CT and MRI imaging to determine pancreatic volume and distinguish fat within the pancreas. Ultrasound has also been used but is not as quantitative and is more operator dependent. Studies of diabetic patients with CT and MRI have consistently shown a decrease in pancreatic volume of 30-55% in Type 1 and 15-30% in Type 2 diabetes (96, 178, 188, 242, 323). Some studies have shown a dependence on the duration of diabetes but others have not. Several studies in which type 3 diabetes or a history of alcoholism have been omitted have shown a smaller loss in pancreatic volume. These changes have been confirmed in a recent meta-analysis of 17 studies (88). The authors noted, however, that many of the individual studies were small and classified as low to moderate quality data. Only type 2 diabetes has shown increased pancreatic fat which reduces the volume of parenchymal tissue from the total volume (178, 188). In some studies, with functional as well as imaging data, the decreased pancreatic volume correlated with decreased function as measured by fecal elastase (242). To date there are no longitudinal studies although this could be done with MRI since there is no ionizing radiation.

2. Effects of diabetes on pancreatic function

Direct measurement of pancreatic juice bicarbonate ion and digestive enzymes in response to secretin and CCK using multi-lumen tube collection has been applied to diabetes. Ewald and Hardt list 9 such studies from 1943 to 1996 (73). These studies all show decreased exocrine pancreatic secretion with a bigger effect seen in Type 1 diabetes. An effect of the duration of diabetes was seen in some (162) but not in other studies (80). Most studies show a bigger effect on amylase than on other digestive enzymes and the smallest effect is on bicarbonate.

Indirect pancreatic function testing on stool samples have allowed study of greater number of patients. The most commonly used test is fecal

elastase measured by an ELISA assay where $<200 \mu\text{g/g}$ is considered evidence for pancreatic exocrine insufficiency (PEI) and $<100 \mu\text{g/g}$ severe deficiency. Elastase is used because it is more resistant to protease digestion although some studies have measured fecal trypsin or chymotrypsin activity which yields similar results relative to controls. In the first large study of more than 1000 diabetics, 40.7% showed fecal elastase levels of less than $200 \mu\text{g/g}$ with 22.9% being $<100 \mu\text{g/g}$ (108). Other studies have reported similar results (74, 163, 222) although the frequency of PEI is lower when patients with Type 3 diabetes were excluded (303, 316). Type 1 diabetics with reduced fecal elastase show a higher frequency of steatorrhea up to 60% although the amount of stool fat is modest (35, 107) and clinical PEI requiring enzyme supplementation is rare (38).

Overall, diabetes is accompanied by decreased pancreatic mass and reduced secretion of digestive enzymes along with a diffuse pancreatic fibrosis characterized by intra-acinar fibrosis whose pattern is distinct from that of chronic pancreatitis. These changes may be the result of reduced number of acinar cells, loss of insulin as a trophic factor or alteration in neural control (207). These authors proposed that these changes be recognized as distinct from chronic pancreatitis and be termed "diabetic exocrine pancreatopathy".

B. Animal studies of the effects of insulin and diabetes on the exocrine pancreas

1. Insulin receptors in the exocrine pancreas

Insulin receptors (IR) on pancreatic acinar cells were first demonstrated by the binding of ^{125}I -insulin in a saturable manner to isolated acini from mouse, rat and guinea pig (156, 263, 282). Scatchard-plot analysis of binding were biphasic and showed high affinity sites with a K_d of about 1.5 nM and capacity of about 10,000 receptors per cell; low affinity sites were much

more numerous with a Kd of 88 nM for mouse and 998 nM for rat. Addition of unlabeled insulin accelerated dissociation from rat acini consistent with negative cooperativity rather than two distinct sites (263). The receptor bound insulin analogs with varying potency (insulin > desdipeptide insulin > proinsulin > desoctapeptide insulin) that was similar to the ability of the analogs to increase protein synthesis in acini from diabetic rats (154). Guinea pig insulin is significantly different from other species and guinea pig acinar receptors bound bovine insulin with a higher affinity than guinea pig insulin or porcine proinsulin (282). Mouse acini were also shown to possess distinct receptors for IGF-I and IGF-II (328).

The localization of insulin binding to acinar and other cells in the pancreas has been demonstrated by light and EM autoradiography. When ¹²⁵I-Insulin was injected intravenously, saturable uptake was observed by the pancreas (19, 46, 261). EM autoradiographs showed silver grains localized both over the plasma membrane and intracellularly in acinar cells. Saturable binding was also observed over duct cells (261). In an *in vitro* study of ¹²⁵I-Insulin binding to rat acini, silver grains from ¹²⁵I were primarily over the plasma membrane at 3 min but by 30 min were primarily intracellular (97). Studies in other cell types have shown that both insulin and its receptor are internalized although the function of internalized insulin is unclear.

Insulin receptors on acinar cells are also subject to regulation. Insulin down regulates its own receptor in a variety of cells, including acinar cells, when they are exposed to high concentrations of insulin through the islet-acinar portal blood system (12, 324). Acini prepared from diabetic mice showed an increased number of IRs compared to normal mice and addition of insulin to 24 hour cultured acini decreased insulin binding (209). Using pancreatic AR42J cells, insulin decreased the biosynthesis of insulin receptors in part by decreasing IR mRNA levels (209, 226). The binding of insulin was also affected by CCK and other secretagogues (228). CCK, carbamylcholine, active phorbol ester

and calcium ionophore (A23187) all decreased high affinity binding without affecting insulin internalization or degradation.

The occupancy of insulin receptors has also been related to the biological effects of insulin on acinar cells. Insulin increased glucose transport (uptake) by acini from normal and diabetic mice (156, 329) with a greater effect on acini from diabetic animals that was seen at lower concentrations of insulin. This greater effect is due both to lower contaminating insulin levels and IR upregulation. In acini from diabetic rats and mice, insulin increased protein synthesis as shown by incorporation of radioactive amino acids (154). Of likely relevance to protein synthesis, insulin rapidly increased the phosphorylation of ribosomal protein S6 which is associated with increased protein synthesis (33, 290). The concentration dependence and analog specificity of these actions of insulin is similar to the data for receptor occupancy (98).

More recently IR have been demonstrated in pancreatic acini by immunoblotting of the beta subunit of the receptor (265). The subunit had an apparent size of about 95 kDa and was essentially absent after deletion of the IR gene in acinar cells. The biological response to insulin in the pancreas of these mice was greatly reduced.

2. Insulin regulation of exocrine pancreas biosynthetic and metabolic effects

Gene expression

Insulin is known to regulate both the amount and activity of a number of anabolic processes and specific metabolic enzymes. In the exocrine pancreas the best studied tissue specific regulation is that of the digestive enzyme amylase which acts on dietary starch and glycogen (325). The pancreatic amylase content is known to decrease by over 90% in experimental diabetes in rats and the fall can be reversed by administration of insulin. This has been studied primarily in rats given alloxan or streptozotocin which induce beta cell death and diabetes (2, 15, 17, 58, 235, 283, 286).

At the same time other digestive enzymes including trypsinogen, chymotrypsinogen and lipase increase slightly and ribonuclease decreases slightly. Amylase also decreases in mouse pancreas in experimental diabetes but by only about 50%. Pancreatic amylase also decreases in the Zucker fatty rat and the ob/ob mouse, well characterized models of insulin resistance (304).

The decrease in pancreatic amylase in experimental diabetes is accompanied by a decrease in amylase synthesis (286). Moreover, insulin increased amylase biosynthesis in rat pancreatic derived AR42J cells (210). The major cause of the decreased amylase synthesis and tissue content is a decrease in amylase mRNA which was first reported by Korc et al (60, 155). The decrease in amylase mRNA could be reversed by insulin. Chymotrypsinogen mRNA showed a small change in the opposite direction and there was essentially no change in salivary amylase or its mRNA. Subsequently, Brannon and colleagues showed that dietary glucose and insulin together regulated pancreatic amylase (*Amy2*) gene expression (306). More detailed information on the mechanism of amylase gene regulation comes from studies in mice. A 30-bp region in the proximal amylase promoter overlapping with the PTF1 binding site present in most pancreatic digestive enzymes contains the insulin-dependent element and can transfer insulin sensitivity to the elastase promoter (134, 140). This regulatory region is not present in all mouse amylase alleles and this can explain why some mouse strains are not as sensitive to diabetes and insulin (57). Unfortunately, there has been little subsequent work defining how insulin receptor signaling regulates the insulin response element.

Membrane transport

Insulin is known to stimulate membrane transport of many substances usually by effects on the amount of or properties of specific transport proteins. The best studied and probably the most important physiologically is the uptake of glucose

into fat and muscle cells that is mediated by the glucose transporter, GLUT4. GLUT4 is present at rest in intracellular vesicles that translocate to the plasma membrane in response to insulin, increasing glucose uptake 5-20 fold. Most other cell types contain GLUT1 that is regulated by another mechanism but to a lesser extent. In mouse pancreatic acini, insulin stimulated the uptake of the nonmetabolizable sugar 2-deoxyglucose (2DG) about two fold (156). A more robust effect of lower concentrations of insulin was seen when acini were prepared from diabetic mice and uptake of both 2DG and 3-O-methyl glucose, a non metabolizable glucose analog, were increased (329). Glucose uptake was not affected by inhibitors of protein synthesis but was reduced by the actin inhibitor, cytochalasin B.

In some tissues insulin also stimulates the uptake of amino acids through effects on specific amino acid transporters. Uptake of amino acids have been studied in many pancreatic preparations. One of the earliest studies using microdissected pieces of mouse pancreas showed that amino acids were taken up and oxidized in preference to glucose (48). Neither CCK or insulin affected uptake and transport did not appear to be separated from protein synthesis. Latter studies used perfused pancreas or isolated acini and showed that the basolateral membranes of pancreatic acinar cells possess 4-5 distinct transporters as measured by physiological studies or gene expression (190, 252). Insulin stimulation studies in the perfused rat pancreas show effects of exogenous insulin and diabetes on two Na⁺-independent transporters, the Asc transporter used by serine (193, 221) and a basic amino acid transporter termed γ^+ for lysine/arginine (215) while no effect was seen on the Na⁺ dependent dependent transporters such as the system A transporter for AIB and glutamine (192). Moreover, increasing glucose in the perfusate which released endogenous insulin had no effect (221). Studies in isolated rat pancreatic acini also showed no effect of insulin on AIB and cycloleucine uptake which are not used for protein synthesis although it stimulated incorporation of leucine into protein

(154). In a more recent study of the mouse pancreas, Rooman et al analyzed the expression of 37 genes encoding transporters and found expression of a number with the highest expression of *slc7a8* and *slc3a2* and confirmed the expression of five by western blot (252).

Protein synthesis

Insulin is known to stimulate protein synthesis by translational effects in many tissues (132). Early studies in the pancreas involved in vivo studies of the incorporation of radioactive amino acids into total protein or specific enzymes of normal and diabetic rodents (45, 61, 157). While most of the studies showed a positive effect of insulin the results are complicated by changes in the precursor pool or changes in the levels of mRNAs. When protein synthesis in mice was quantitated by autoradiography, there was more incorporation into peri-insular acinar cells than into tele-insular acinar cells (7). This difference was lost following treatment with streptozotocin and the authors ascribed it to insulin. One study overcame some of these issues by changing plasma insulin and glucose in vivo but measuring protein synthesis in vitro using pancreatic lobules incubated in a constant medium (2). It showed that either glucose infusion in vivo or treatment with a sulfonylurea drug both of which stimulate insulin release increased protein synthesis by 25 – 40%. When Zucker fatty rats were studied as a model of insulin resistance, overall pancreatic protein synthesis was reduced by nearly 50% (305). There was considerable difference in synthesis between different digestive enzymes separated by 2-D-gel electrophoresis. A morphological study of prolonged diabetes in rats showed gross abnormality in the secretory pathway 28 days after STZ treatment that was partially reversed by insulin administration (333). However, shorter studies have not shown significant structural alterations 1 week after STZ other than the appearance of cytoplasmic lipid droplets (154).

More recent studies have been able to overcome some of the methodological issues by measuring the effects of insulin over short times to prevent changes in mRNA and under conditions where the precursor pool is large and constant (264). In vitro studies have used isolated pancreatic acini under dilute incubation to keep the precursor pool constant. Insulin stimulates the incorporation of multiple different amino acids (leucine, methionine, phenylalanine) in isolated acini from diabetic rats (153, 154, 160, 227). Similarly, insulin increased methionine incorporation into total protein and immunoprecipitated amylase in rat pancreatic derived AR42J cells (210). The effect of insulin on both cell types occurred over concentrations from 30 pM to 100 nM and was mediated by the insulin receptor as insulin analogs stimulated in parallel to their ability to bind to the insulin receptor (154, 227). Insulin was also shown to have nonparallel effects on different digestive enzymes and structural proteins such as myosin and LDH (227). Although the mechanism of insulin signaling is well studied in a number of target tissues especially liver, fat and muscle, only a few studies have been carried out in the exocrine pancreas. The main signaling pathway regulating protein synthesis is the mTOR pathway and this pathway has been documented in pancreatic acinar cells primarily in mediating the actions of CCK and acetylcholine to stimulate digestive enzyme synthesis (266, 326). Insulin has been shown to activate S6 kinase and S6 phosphorylation downstream of TORC1 in rat and mouse acini (33, 290). Akt is upstream of mTOR and insulin activates the phosphorylation of Akt on S473 and T308 in rat acini (20). This action appeared mediated by PI3K. That these actions are important physiologically is shown by over a 50% reduction in mTOR pathway activation after feeding in mice without acinar cell insulin receptors (265).

Secretion

The effects of insulin administration and diabetes on pancreatic exocrine secretion have been studied in a number of species and systems

ranging from intact awake animals down to isolated acinar cells. The more isolated systems have better defined parameters but lack neural control and other integrative aspects found in the intact organism.

In vivo studies have largely been carried out in rats with some studies in dogs and other species and often have compared streptozotocin (STZ) treated and intact animals. STZ and alloxan treatment damage islets thus lowering insulin levels and leading to hyperglycemia. In STZ-diabetic rats pancreatic juice flow has been reported to be moderately increased (18, 241, 285). In two studies this effect was reversed by transplanting syngeneic islets into the liver (53, 168). However, in mice STZ treatment or genetic models of diabetes leads to reduced juice flow (265), and in sheep, alloxan treatment led to a substantial decrease that could be restored by insulin treatment (243). In all of these studies the effects of the diabetic state on plasma glucose and lipids is not clear. The effects of CCK on digestive enzyme secretion in diabetes are complicated by changes in the pancreatic content of specific digestive enzymes. The concentration of secreted amylase is decreased and trypsin increased although both respond to CCK (18, 285). The most valid results may be in animals with chronic pancreatic fistulas where juice can be collected in the unanaesthetized state but such studies have not been carried out in diabetes.

Other studies have focused on the effects of insulin in normal animals with intact islets. When a high concentration of insulin (4 U per 100 gm) was injected into the femoral vein, subsequent pancreatic stimulation by CCK was potentiated (137). In another study, insulin (1U as a bolus) induced hypoglycemia, increased fluid flow and increased amylase and total protein output; this effect was blocked by atropine and ascribed to hypoglycemia-induced vagal cholinergic activation (241). In a third study an intravenous infusion of insulin also increased pancreatic secretion (76). Not all studies however have reported this effect (284). In a different approach using

unanaesthetized rats, IV injection of rabbit anti-insulin serum but not control serum blocked the pancreatic response to a liquid meal and to exogenous CCK or secretin stimulation (167). In a study in conscious dogs which secrete a high bicarbonate pancreatic juice, most of which comes from the ducts, insulin administration diminished secretin stimulated bicarbonate secretion and this effect was blocked by prior pancreatic denervation (21). This study illustrates the complexity of administering insulin in vivo and show that some of the effects of high dose insulin in vivo are mediated by neural pathways. However, overall they suggest a positive effect of insulin on pancreatic exocrine secretion.

Studying an in vitro pancreas preparation removes the effects of plasma glucose and the brain initiated neural control. While some studies have been carried out with isolated pancreas segments from animals with thin pancreas, the perfused pancreas provides better oxygenation and when single pass perfusion is used the secretion of both endocrine and exocrine secretions can be separately measured. Because the islets are present in their normal position, they can be stimulated independent of the exocrine pancreas and the islet hormones will reach the exocrine cells by local diffusion and even more importantly by the islet-acinar portal system. Most studies of the perfused normal rat pancreas or isolated pancreatic segments incubated with normal glucose have shown that exogenous insulin has little or no effect on basal fluid and protein secretion but potentiates the secretory effect of CCK, ACh, or secretin (89, 109, 135, 137, 169, 240, 257, 258, 277). In STZ induced diabetic animals with high plasma glucose, the *in vitro* response to secretin, and CCK was reduced compared to normal rats (229, 230). This change could be partially reversed by treatment with insulin. To study the effect of endogenous insulin, investigators have used a low plasma glucose background and then a pulse of high glucose to stimulate insulin release; this endogenous insulin which must reach the acinar cells by the islet-acinar portal system increased

secretion of fluid, protein and amylase in response to CCK or ACh (89, 257, 258). This effect was induced only by sugars that stimulate insulin secretion and could be blocked with epinephrine or somatostatin which block glucose induced insulin release. In an alternative approach, Chey and colleagues added anti-insulin antibody to the perfusate in the rat or dog perfused pancreas and showed that this resulted in reduced juice, bicarbonate and protein secretion (165-167). All of this data is consistent with insulin having an action on acinar and duct cells to facilitate secretion. However, other studies have reported that both high glucose and exogenous insulin inhibits CCK stimulated amylase secretion in the mouse (47) or caerulein-stimulated perfused rat pancreas (32). In the perfused cat pancreas, insulin had no effect on the basal fluid or enzyme secretion (332). While a stimulatory effect of insulin on acinar cells is consistent with the presence of insulin receptors on acinar and duct cells and the ability of insulin to act on isolated pancreatic acini (see below), other studies have suggested effects within the islet can explain much of the actions of insulin. In the studies of immunoneutralization of insulin in perfused rat and dog pancreas, Chey's group showed that insulin antibody increased the concentration of somatostatin and pancreatic polypeptide in the venous effluent. In their rat study, addition of an antisomatostatin antibody partially reversed the effect of the anti-insulin and the addition of somatostatin partially reversed the effect of combined stimulation by CCK and secretin (166, 169). Using a perfused canine pancreas, insulin antiserum blocked secretion but when SS and PP antibodies were added together, the effect on fluid and bicarbonate was fully reversed and the inhibition of protein secretion was partially reversed (165). These investigators concluded that the inhibitory effect of insulin antisera was mediated by the local release of and action on the exocrine pancreas of somatostatin and PP (165). In a related study, Nakagawa et al concluded that the net effect of islet peptides on the exocrine pancreas was negative because exocrine

secretion was greater with retrograde than anterograde perfusion (219). Thus the action of insulin could be mediated at least in part by suppressing the secretion of inhibitory islet peptides. One study of duct function showed that insulin increased pancreatic juice secretion and that this effect was blocked by ouabain (109).

Isolated pancreatic acini and ducts can be used to study cellular function in the absence of neural, hormonal and islet control. Isolated acini are exquisitely sensitive to CCK, acetylcholine, and bombesin, and respond through an increase in intracellular Ca^{2+} to increase digestive enzyme secretion. Acini also respond through an increase in cyclic AMP to secretin and VIP which can increase enzyme secretion or potentiate the actions of agonists that mobilize Ca^{2+} . Isolated acini from STZ induced diabetic rats show reduced secretion of amylase and ribonuclease in response to CCK and cholinergic agonists (233-235, 239). This decreased secretion is also seen with alloxan-induced diabetes and can be reversed by treatment of the animals with insulin. One cause of the decreased secretion is a decrease in the synthesis and content of digestive enzymes. When secretion is normalized to content and expressed as per cent of content released per 30 min, maximal secretion is similar but the dose response to CCK is shifted to the right while the response to carbachol is similar. Thus, there is also an effect on CCK receptors which was confirmed by radioactive binding of CCK showing changes in affinity and capacity of the two affinity states (233). Interestingly, RT-PCR of the CCK1 receptors showed no change in pancreatic receptor mRNA in rat STZ induced diabetes (255). Acinar cell post receptor signaling is also altered in diabetes with changes in CCK-induced IP_3 formation (40, 149, 255). This is accompanied by changes in the amount and phosphorylation of IP_3 receptors. The increase in intracellular free Ca^{2+} measured in suspension or single cells is also reduced in diabetes (239, 255).

An effect of insulin in vitro on both diabetic and normal rat acini has also been demonstrated. An effect of insulin to increase amylase release was seen as early as 30 min and increased to a maximum at 2 h (234). Over this time the number and affinity of CCK receptors was also changed. In another study in acini from normal rats, insulin after 90 min potentiated the secretion in response to CCK plus secretin but had no effect on either alone; this potentiating effect of insulin was inhibited by the $\text{Na}^+ - \text{K}^+$ ATPase inhibitor, ouabain (197). Insulin also has been shown to directly activate the plasma membrane Ca^{2+} ATPase (PMCA) in rat (191).

the mechanism of these effects are not fully established. Moreover, all studies have been carried out in rats and rat tissue and the results need to be extended to other species. The cellular sites where insulin acts on pancreatic acinar cells are shown in **Figure 1**. Finally, data is needed from isolated ducts to establish whether there is a direct effect of insulin on ductal bicarbonate secretion.

C. Effects of insulin on pancreatitis and other pancreatic diseases

1. Clinical and animal studies linking diabetes with pancreatitis

Sites of Insulin Action on Pancreatic Acinar Cells

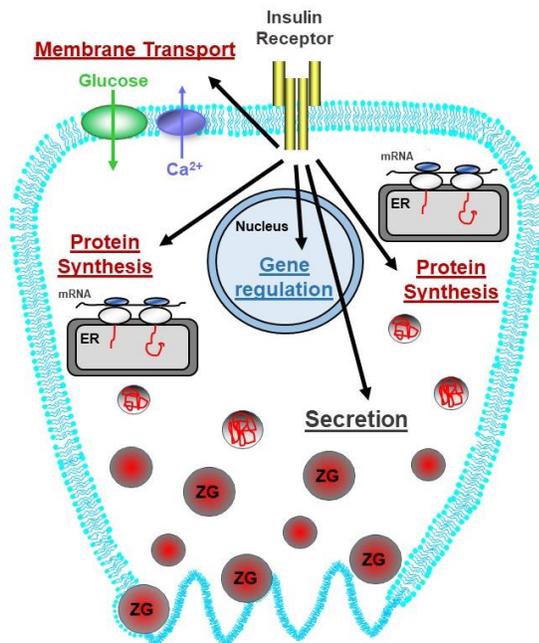


Figure 1. Sites of insulin action on pancreatic acinar cells. Insulin has receptor dependent actions to regulate protein synthesis at the translational level, gene expression at the transcriptional level, membrane transport of glucose and calcium, and potentiation of digestive enzyme secretion. Not all of the steps between receptor occupancy and the end biological effect are known and most of the data is from rodent pancreas. (See text for details and references).

There is emerging evidence from clinical studies (93, 99, 106, 202, 250, 271) and animal studies (111, 114, 338) that pre-existing diabetes may predispose, increase the risk or make pancreatitis more severe. This implies that endogenous insulin may have a protective role during pancreatitis. Type-2 diabetics have an ~3 fold increased risk of developing acute pancreatitis (AP) (93, 220, 250, 271), which could be explained by a loss of direct protection of insulin on pancreatic acinar cells, due to insulin resistance. Pre-existing diabetes increases the severity of acute pancreatitis (202) and diabetes increases the mortality in patients with chronic pancreatitis (148, 172). Around half of type-1 diabetic patients exhibit lesions within the exocrine pancreas that are reminiscent of chronic pancreatitis (106).

Moreover, acute pancreatic patients with hyperglycemia are at higher risk of multiple organ failure (199). Hyperglycemia frequently accompanies severe acute pancreatitis and is used in the Ranson score as a predictor of disease severity (246). Furthermore, the incidence of AP is higher among type-2 diabetics compared to the normal population and the risk of AP was reduced among diabetic patients treated with insulin or metformin compared to those treated with other drugs such as sulphonylurea based antidiabetic drugs (99).

These studies along with other metabolic effects of insulin on isolated acinar cells indicate that insulin can directly affect acinar cell secretion. However,

For many years there have been numerous anecdotal histological observations of the pancreas in animals that the acinar cells surrounding the islets (peri-islet acinar cells) are morphologically distinct from acinar cells distant from the islets. This was further investigated in L-arginine-induced experimental animal models of pancreatitis in which peri-islet acinar cells remained relatively intact compared to distal injured acinar cells, (111, 113, 114, 296). This peri-islet acinar cell protection was abolished in streptozotocin (STZ)-induced diabetic rats, with impaired insulin secretion (111, 112, 114). These studies suggest that insulin release has a paracrine protective role in the pancreas. Moreover, in addition to the acute injury, the regeneration of exocrine pancreatic tissue was abolished in diabetic rats and restored following the administration of exogenous insulin (111, 113, 114, 296). This was further investigated in the seminal study by Zechener et al 2012 (338), in which caerulein-induced pancreatitis was aggravated in streptozotocin (STZ)-induced type-1 diabetic mice (338). Specifically, they showed that numerous markers of the acute phase of pancreatitis injury (within 24 hours) were markedly potentiated; including plasma amylase, lipase and trypsinogen, pancreatic edema (wet/dry weight ratio), pancreatic histological tissue injury score (H&E), inflammation and cell death. In addition, regeneration of the pancreas (7 days later) was delayed (338). Moreover, this diabetic-induced potentiation of pancreatitis phenotype was partially corrected by exogenous administration of insulin (slow release pellet implant). They also suggested that the mechanism for this more severe pancreatitis phenotype in STZ-induced diabetic mice was due at least in part to depleted pancreatic regenerating islet-derived 3 β (REG3 β) peptide, which has important anti-inflammatory and antimicrobial properties. REG3 β is upregulated during pancreatic injury and is suggested to act as an acute emergency program to circumvent the inflammatory response during pancreatitis (43, 94, 312, 340). However, REG3 β expression was found to be severely blunted in the pancreas of STZ-

induced diabetic mice, suggesting that this may contribute to the more severe pancreatitis phenotype (338).

2. Insulin protection during cellular models of pancreatitis

From a clinical perspective, and to some extent the diabetic animal studies, it is very difficult to separate the confounding effects of hyperglycemia or reduced systemic effects of insulin from a loss of direct insulin protection of acinar cells. This is important because hyperglycemia is associated with a more severe pancreatitis, by providing a pro-inflammatory environment and by facilitating sepsis (251). Moreover, insulin itself exhibits anti-inflammatory properties (159), therefore the systemic loss of insulin secretion or insulin effectiveness would be predicted to promote systemic inflammation. However, studies using acutely isolated pancreatic acinar cells provide compelling evidence that insulin directly protects acinar cells from cellular injury induced by pancreatitis-inducing agents, such as oxidative stress (H₂O₂) or the alcohol/fatty acid metabolite, palmitoleic acid (POA) (cellular models of acute pancreatitis) (191, 262). Specifically, insulin markedly attenuated ATP depletion, the inhibition of plasma membrane calcium ATPase (PMCA) which transports Ca²⁺ out of cells, cytotoxic Ca²⁺ overload and necrotic cell death. This protection was partially PI3K/Akt-dependent and due to an acute metabolic switch from mitochondrial to glycolytic metabolism (191, 262). Consistent with this, insulin enhanced PMCA inhibition by glycolytic inhibitors and abolished PMCA inhibition by mitochondrial inhibitors (191). Therefore, this switch to glycolysis appears to maintain cytosolic ATP concentration sufficiently to fuel the PMCA and thus prevent cytotoxic Ca²⁺ overload, even in the face of impaired mitochondrial function.

The most likely downstream signaling pathways responsible for insulin's protective effects during pancreatitis are likely to be mediated by tyrosine kinase or PI3K/Akt. It's also interesting to note that

several related growth factors (GF), that also couple to tyrosine kinase and PI3K/Akt, similar to insulin, are also reported to be protective in animal models of pancreatitis (50, 318, 319). These include insulin-like growth factor (IGF-1), fibroblast growth factor (FGF), hepatocyte growth factor (HGF) and epidermal growth factor (EGF). Although, altered expression of signaling proteins and metabolic enzymes may contribute to insulin's protection *in vivo*, most of the protective effects of insulin observed in acinar cells occurred over a relatively short-term (15-30 minutes), suggesting a more rapid effect of post-translational effects, such as tyrosine kinase or PI3K/Akt phosphorylation.

Arguably, the most important mechanism for insulin's protection is the regulation of glycolytic ATP. Glycolytic flux is primarily regulated by the activity of phosphofructokinase-1 (PFK1), which catalyses the conversion of fructose-6-phosphate (F6P) to fructose-1,6-bisphosphate (F1,6BP) and represents the first rate-limiting irreversible step in glycolysis. Insulin has been shown to lead to the Akt-mediated phosphorylation and direct activation of phosphofructokinase-2 (PFK2); otherwise known as phosphofructokinase-fructose bisphosphatase (PFKFB). PFKFB consists of four separate bi-functional glycolytic enzymes (PFKFB1-4), with varying catalytic and functional activities (51). PFKFB catalyses the conversion of F6P to fructose-2,6-bisphosphate (F2,6BP), via their kinase activity, but also the reverse reaction, by converting F2,6BP back to F6P, via their bisphosphatase activity (51). F2,6BP is a potent positive allosteric activator of PFK-1, which maintains high glycolytic flux (14). Therefore, Akt-mediated phosphorylation of PFKFB2 may represent the major molecular mechanism by which insulin increases glycolytic ATP supply in the face of impaired mitochondrial metabolism during acute pancreatitis.

3. The effect of insulin on the gut microbiome-pancreatitis link

Severe acute pancreatitis is frequently accompanied by infected pancreatic necrosis and systemic bacteremia or sepsis (37). The source of the bacteria is thought to be from "leaky" gut, particularly the colon, which houses a large reservoir of pathogenic and commensal bacteria (317). This is caused by gut dysbiosis, inflammation, altered mucus secretion and the consequent loss of gut barrier function and bacterial translocation into the blood (37). The gut microbiome consists of a delicate balance of trillions of bacteria from thousands of different bacterial species that can be broadly categorized into "good" (anti-inflammatory) or "bad" (pro-inflammatory). Moreover, bacteria can aid in the breakdown and absorption of undigested carbohydrates and produce numerous beneficial anti-inflammatory metabolites, such as the short chain fatty acids (SCFAs) butyrate, acetate and propionate that promote epithelial integrity and gut barrier function (297).

This delicate balance of the gut microbiome and bacterial diversity is maintained by numerous antimicrobial peptides (AMPs) secreted mainly from the Paneth cells within the crypts of Lieberkuhn of the small intestine (8). However, several studies show that AMPs are secreted from pancreatic acinar cells, which may contribute to maintaining a healthy gut microbiome. These include the related C-type lectin family members; lithostathine (REG1 α/β) (49), REG3 family members (REG3 $\alpha/\beta/\gamma$) - sometimes referred to as pancreatitis-associated peptide (PAP)/hepatocarcinoma-intestine-pancreas (HIP) (43, 94, 312, 340), cathelicidin-related AMP (CRAMP) (4), and defensins (268).

PAP was originally discovered in pancreas homogenates, secretory granules and in the pancreatic juice during experimentally-induced acute pancreatitis in rats, but was absent in control rats (139). PAP expression was also increased in pancreatic acinar cells in response to both acute and chronic pancreatitis (232). Moreover, PAP/REG3 β expression is regulated by dietary carbohydrates (64) and is blunted in diabetic mice

(338), suggesting that insulin regulates the expression of PAP/REG3 β . Therefore, during pancreatitis the loss of PAP/REG3 β secretion into the gut may accentuate the gut dysbiosis, inflammation and loss of barrier function and bacterial translocation, thereby further contributing to the severity of acute pancreatitis.

It is also possible that gut dysbiosis in diabetics may be caused by reduced pancreatic secretion of amylase. Amylase is a highly abundant digestive enzyme that breaks down starch in the gut and its expression and secretion is controlled by insulin and high carbohydrate diet (248) and is reduced in diabetic animals (154). Such loss of amylase secretion may also alter the gut microbiome, due to huge amounts of undigested starch entering the colon leading to overgrowth of bacteria that break down un-digested starch (*Bacteroides spp*). However, this has never been fully and specifically investigated and it remains unclear whether reduced amylase per se in the gut would be beneficial or detrimental. Even though pancreatic enzyme insufficiency (PEI) leads to numerous comorbidities that might be explained by an altered gut microbiome, disentangling the specific effects of reduced amylase secretion from the loss of other digestive enzymes would be difficult.

It is also interesting that the gut microbiome is able to signal to and thus contribute to the maintenance of a healthy inflammatory and immune landscape within the pancreas, and when disrupted may ultimately lead to autoimmune type-1 diabetes (289). Specifically, SCFAs, such as butyrate, released from gut bacteria are able to leak into the circulation and reach sufficient concentration to promote the secretion of CRAMP from pancreatic β cells. CRAMP induced a positive immunoregulatory phenotype in pancreatic resident macrophages by promoting the production of anti-inflammatory cytokine, TGF β , to maintain immune homeostasis via Treg induction. However, the loss of SCFAs following gut dysbiosis disrupts this process, leading to reduced CRAMP secretion which promotes a pro-inflammatory environment in

which activated macrophages secrete TNF α and the ultimate autoimmune destruction of pancreatic β cells and the consequent Type-1 diabetes (289). This therefore suggests a complex reciprocal regulation between the gut microbiome, the exocrine and the endocrine pancreas

4. Insulin as a therapy to treat acute pancreatitis

Insulin therapy has been used to specifically treat hypertriglyceridemia (HTG)-induced pancreatitis with promising outcomes (125, 247). HTG occurs when plasma lipids exceeds 1,000 mg/dL (normal range, 101-150 mg/dL) (182). HTG-induced pancreatitis is relatively rare, accounting for 2.3% to 10% of all cases of acute pancreatitis, but is a well-documented etiological risk factor leading to severe disease (307). The rationale for using insulin therapy to treat HTG-induced pancreatitis is that it lowers plasma triglycerides, by activating lipoprotein lipase (convert triglycerides into free fatty acids) and inhibiting the hormone-sensitive lipase (liberates adipocyte triglyceride), thereby limiting inflammation (66). However, given the evidence presented above, it's entirely possible that the beneficial effects of insulin therapy in HTG-induced pancreatitis patients could be due to a direct protection of acinar cells.

Insulin is also used as the standard of care for all critical care patients, including those with severe acute pancreatitis, with the aim of targeting hyperglycemia associated with the acute phase of injury, which facilitates inflammation and sepsis (287). There have been numerous clinical trials and meta-analyses testing the effectiveness of intensive insulin therapy in critical care patients and some studies question whether there is any overall patient benefit (101, 181, 322, 334-336). However, this is likely because in patient groups receiving insulin, fewer patients die from septicemia, but more die from the complications of inadvertent hypoglycemia, an independent risk factor of mortality (67, 126, 158, 310).

However, given the direct protective effect of insulin on acinar cells described above there is a strong rationale to test high dose insulin infusion with very tight moment-to-moment glucose control to specifically target the acinar injury. This could be achieved using the hyperinsulinemic euglycemic clamp with automated insulin minipumps combined with continuous closed loop subcutaneous glucose monitoring devices (170). It could be argued that there is a greater requirement for high dose insulin because pancreatic acinar cells receive a portal blood flow (175) with ~10 times higher insulin concentration than the systemic circulation (218, 219). Furthermore, stress hormones, such as adrenaline, cortisol and glucagon, and inflammatory cytokines (TNF α and IL-1 β) reduce tissue sensitivity of insulin, so a higher dose of insulin may be necessary to overcome this. Moreover, high dose insulin infusion (8 mU/kg/min; adjusted for surface area to weight ratio) with tight physiological glucose control has been tested in healthy human volunteers during endurance exercise studies with no reported adverse effects (189).

IV. Action of other islet hormones/peptides on the exocrine pancreas

A. Glucagon

Glucagon was originally identified in pancreatic extracts as a hyperglycemic-glycogenolytic factor that came from the α cells of the pancreatic islets (102, 293). Foa and colleagues showed by cross circulation experiments in dogs that hypoglycemia induced by insulin triggered glucagon release which causes hyperglycemia in the recipient animal (78). The subsequent development of a radioimmunoassay for glucagon by Unger made more detailed studies of the physiology and pathophysiology of glucagon possible (309).

Glucagon is a 29 amino acid peptide derived from proglucagon in islet α cells through the tissue specific processing by prohormone convertase 2

(PCSK2) (87). By contrast, in intestinal enteroendocrine cells proglucagon is processed to GLP-1, GLP-2, oxyntomodulin, and glicentin (171). The major role of glucagon is to antagonize the effects of insulin and maintain plasma glucose homeostasis by promoting hepatic gluconeogenesis and glycogenolysis and inhibiting glycogen synthesis (25). The major regulators of glucagon secretion by islet α cells are glucose which inhibits and amino acids as well as parasympathetic and sympathetic nerves which stimulate glucagon release. The suppression by high glucose, however, is not direct but mediated by insulin/GABA secreted by islet β cells. Somatostatin also suppresses glucagon secretion.

The effect of exogenous glucagon on exocrine pancreatic secretion has been studied in vivo with a consistent effect of high concentrations of purified crystalline glucagon to inhibit exocrine secretion of fluid, bicarbonate and protein stimulated by food, CCK or secretin in dogs (65, 123, 152, 276), cats (151), rats (1, 22, 272), and humans (42, 52, 105). The mechanism of this inhibition is unclear in these studies. In vitro, studies have been carried out in the perfused pancreas, pancreatic segments and lobules with mixed results (25). With the development of isolated pancreatic acini and acinar cells, natural purified glucagon was shown to stimulate amylase secretion and increase cyclic AMP in rat, mouse and guinea pig acini (237, 278, 279). However, the stimulatory principle did not elute with synthetic glucagon so its nature is unknown. Most importantly, synthetic glucagon has no effect on amylase secretion by isolated acini (10, 237). Glucagon receptor mRNA has been identified in the pancreas but not in isolated acini or ducts (63, 104). Thus, these studies do not support a direct effect of glucagon on acinar cells. Whether the islets or the nervous system is involved is not yet established.

B. Somatostatin

Somatostatin (SS) was originally identified in hypothalamic extracts as a factor able to inhibit

growth hormone release and was subsequently purified as a cyclic peptide containing 14 amino acids (SS-14) (27). A second form extended at the amino terminal and containing 28 amino acids (SS-28) was later characterized (244). Subsequently, somatostatin was found to be widely distributed in the body including other regions of the brain, the small intestine, pancreatic islets and the stomach. For information on the mRNA sequence and the somatostatin precursor see (208). Outside the nervous system, including islets, somatostatin is produced in D cells and is now considered to be both a hormone and a paracrine regulator and generally acts as an inhibitor of specific physiological processes such as gastrin secretion in the stomach and insulin secretion in the islet. The effect of somatostatin is mediated by specific receptors which most often act to inhibit adenyl cyclase but can also regulate ion channels and activate tyrosine phosphatase (249).

In all species studied plasma somatostatin goes up after a meal; in humans the basal concentration is about 10 pM and this doubles after eating (103, 343). The majority of circulating SS comes from the gut and not the islets (295). However, somatostatin released from islet D cells can have direct effects on other islet cells and pancreatic exocrine cells. Somatostatin release is controlled by cholinergic and adrenergic nerves as well as gastrointestinal hormones including CCK, secretin and VIP (208). The half-life of SS-14 in plasma is 1-2 min while that of SS-28 is 3-4 min (313).

Pancreatic exocrine secretion of fluid and enzymes is inhibited by in vivo administration of SS-14 or SS-28 in conjunction with stimulation by meal feeding or administration of CCK and/or secretin in dogs (23, 138, 147, 291, 292, 331), rats (41, 79), cats (6), rabbits (203), and humans (56, 69, 120). Additional studies using long acting SS analogs such as Octreotide (SMS201-995) and RC160 have shown similar results (141, 150, 194, 294). That an effect of endogenous SS release on the pancreas may have physiological importance is suggested by the fact that exogenous SS

mimicking postprandial levels is able to inhibit insulin and amylase secretion (103). Moreover, immunoneutralization of circulating SS leads to an enhancement of CCK stimulated pancreatic amylase secretion (311).

The site at which SS inhibits exocrine pancreatic secretion and its physiological importance is unclear. Suggested sites include the central or peripheral nervous system, within the islet through effects on insulin secretion and at the level of pancreatic exocrine cells. It is of course possible that SS acts at more than one site. Because this review focuses on regulation of exocrine pancreas by islet peptides and because somatostatin receptors have been identified in the exocrine pancreas that possibility will be considered first.

Using iodinated analogs of SS-14 and SS-28, high affinity binding sites with the characteristics of receptors have been identified in isolated pancreatic acini, pancreatic membranes and purified plasma membranes (71, 259, 298, 339). Covalent crosslinking studies showed that the binding protein was a 90 kDa glycoprotein (259). Saturable binding sites were also demonstrated in the perfused rat pancreas with autoradiography showing uptake by islets and acinar cells with the acini showing the highest density (89). Molecular cloning has identified 6 different SS receptors, SSRT1- SSRT5 with SSRT2 having two subtypes (249). All of these are 7 transmembrane proteins that are G protein coupled whose action is mediated by G_i/G_o (164). SSR2 and SSR5 appear to be the main SS receptor isoforms in acinar and islet cells although further work is needed (26, 124).

Studies directed at actions of somatostatin on pancreatic exocrine cells have primarily been carried out using isolated pancreatic acini which have been separated from islets. SS-14, SS-28 and synthetic analogs have consistently been shown to inhibit cAMP formation through a pertussis toxin sensitive mechanism and in most cases to inhibit amylase secretion stimulated by

VIP or secretin which act through cAMP (72, 127, 196, 260, 281). However, most studies reported no inhibition by somatostatin of amylase release stimulated by CCK or cholinergic analogues (72, 127, 214, 280). Rather SS inhibited the potentiating effect of secretin or VIP on CCK stimulation (196, 224). This effect whose size is species-dependent may explain a portion of SS inhibition in vivo but it does not appear to be a major effect. Moreover, it is not clear if it involves islet SS or systemic SS.

The major in vitro technique that allows study of islet SS on the exocrine pancreas is the isolated perfused pancreas where secretion of both islet hormones and exocrine secretion can be measured. Insulin in the perfused pancreas potentiates CCK stimulated exocrine secretion and somatostatin has been established to inhibit both exocrine secretion and insulin secretion (70, 89). In the perfused rat pancreas, high glucose is known to induce secretion of both insulin and SS, and a SS antagonist enhanced amylase secretion induced by glucose plus CCK (238). Depleting SS with cysteamine pretreatment also enhanced CCK stimulated secretion which could be inhibited with exogenous SS. Interestingly, endogenous SS did not modify exocrine secretion stimulated by CCK alone (213, 238). In the perfused pancreas SS also appears to inhibit duct function as fluid secretion stimulated by secretin was potentiated by insulin and inhibited by somatostatin in a manner dependent on Na⁺- K⁺ ATPase function (109).

The other proposed locus of somatostatin action to inhibit the exocrine pancreas is at the level of efferent neural control which is initiated in the dorsal motor nucleus of the vagus (DMV) and travels through the vagus nerve to reach pancreatic parenchymal cells. Studies suggesting inhibition at a central vagal site include the finding in rats that somatostatin inhibits the action of 2-deoxyglucose, a known central vagal stimulator (173) and that microinjection of somatostatin into the DMV inhibits pancreatic secretion evoked by CCK or 2DG (174). However, in dogs and rats,

other investigators have reported that somatostatin still blocked CCK stimulated secretion after complete pancreatic denervation (29, 269). These and other authors concluded that the inhibitory action of somatostatin is not dependent on the extrinsic nervous system but that the intrinsic nervous system could be involved (214).

C. Pancreatic Polypeptide

Pancreatic polypeptide (PP) was discovered as a contaminant in the purification of insulin in 1975 (144). It contains 36 amino acids and is part of a family of peptides that includes peptide YY (PYY) and neuropeptide Y (NPY) and has about 50% homology to these other peptides (301). The biologically active part of the molecule is in the carboxyl terminal and this part of the molecule extends out from the main globular portion (95). PP is immunogenic and immunohistochemistry has localized it in the islets to a specific cell type originally known as F cells, and now referred to as PP cells (77). These cells are most abundant in the original ventral lobe of the pancreas and some are present outside the islet in the duct epithelium. Small amounts of PP are found in other tissues including the brain (122).

In humans fasting pancreatic polypeptide plasma levels are 10-30 pM, they increase rapidly after feeding and remain elevated for 4-5 hours. The vagal nerve is the main stimulator of PP secretion and secretion can be blocked with atropine. Electrical stimulation of the vagus, sham feeding, 2-deoxyglucose and insulin-induced hypoglycemia all stimulate PP secretion in a vagal dependent manner (270, 327). The half-life of PP in plasma is about 6 minutes. Reported actions of PP include effects on the GI tract, metabolism, most notably reversal of hepatic insulin resistance, and as a satiety factor (327). The latter is based in part on Prader-Willi syndrome where loss of PP secretion is associated with obesity (342). The actions of PP are mediated by specific receptors that belong to a family of receptors that bind NPY, PYY and PP (200). The various receptors are denoted by a capital Y with a numerical subscript. The Y₄

receptor has specificity for PP with a high affinity and a hundred-fold lower affinity for PYY.

Purified bovine PP was shown by Lin et al in 1977 to reduce exocrine pancreatic secretion in dogs with pancreatic fistulas (179). This was confirmed by Taylor et al who showed that inhibition of exocrine secretion occurred at doses of porcine PP that raised plasma levels less than seen after a meat meal (302). Similar actions in dogs have been reported by others (16, 39, 185). Shiratori et al. showed a similar effect of human synthetic PP to inhibit canine pancreatic secretion and also showed that immunoneutralization of endogenous PP enhanced both interdigestive and postprandial secretion (274). Similar effects of exogenous PP have been reported in humans (3, 100) and in rats (186, 245).

Although PP acts to inhibit pancreatic secretion *in vivo*, this effect appears to be indirect as exogenous PP had no effect on amylase release from isolated rat or mouse pancreatic acini (92, 186), the perfused cat pancreas (143), or incubated uncinata pancreas of young rats or pancreatic fragments (143, 186). Binding studies with ¹²⁵I-PP also failed to reveal high affinity binding sites on rat pancreatic acini. Although this lack of *in vitro* effects is generally accepted (301), there are several differing reports all using isolated rat pancreatic acini showing a small amount of inhibition (133), stimulation by high concentrations of human PP (59), and inhibition of carbachol but not CCK stimulation by bovine PP (236). Some of these effects could possibly have been due to contaminants in purified PP.

More recent studies have focused on a neural locus for the action of PP to inhibit pancreatic exocrine secretion. Most studies indicate a site of action in the brain stem. Receptors for PP are present in the area postrema, the nucleus tractus solitarius (NTS) and the dorsal motor nucleus of the vagus (320, 321) and intravenous PP inhibits pancreatic enzyme secretion in the rat stimulated with 2-deoxyglucose which acts centrally (245).

More definitively, PP microinjected into the DMV in a site specific manner inhibited pancreatic secretion (231). PP directly spritzed on individual DMV neurons revealed a subset where PP reduced postsynaptic currents (30). This finding suggests that PP in the circulation gains access to the brain through the area postrema and reaches the adjacent DMV where it inhibits vagal excitatory output to the pancreas (217). As an alternative neural site for PP inhibition, Jung et al presented data that rat PP inhibited potassium stimulated amylase release and the presynaptic release of acetylcholine in rat pancreatic slices (136). They suggested that PP acts on postganglionic cholinergic neurons to prevent acetylcholine release. The function of inhibition of pancreatic secretion by PP is unclear although several authors have suggested it is to prevent overstimulation of the pancreas.

D. Adrenomedulin

Adrenomedulin (AM) is a 52 amino acid peptide that was isolated from a human pheochromocytoma and has slight primary homology but stronger tertiary resemblance to calcitonin gene related peptide (CGRP). When injected intravenously, AM causes a potent and long lasting hypotensive effect in anesthetized rats (145, 146). AM is present in various organs but most abundantly in the adrenal medulla. It is present diffusely in endocrine cells of the pancreatic islet but most abundantly colocalizes with PP cells where it is present in secretory granules (195). These authors also showed that it is a strong inhibitor of insulin secretion both *in vivo* and with isolated islets. The AM receptor is made up of a previously orphan receptor, the calcitonin receptor-like receptor (CLR) combined with a receptor-activity-modifying protein (RAMP) (211). There are two AM receptors, AM1 which includes CLR and RAMP2 and AM2 which is made up of CLR and RAMP3; the CGRP receptor is CLR plus RAMP1 (110). In most cells that respond to AM, there is an increase in cAMP (121). In aortic endothelial cells, AM stimulates two signal

transduction pathways that increase cAMP and mobilize Ca^{2+} (273).

Because AM released from PP cells might affect the exocrine pancreas via local blood flow, Tsuchida et al studied the effect of AM on pancreatic acini (308). Radio-iodinated AM was shown to bind to pancreatic acini in a manner inhibited by picomolar concentrations of AM but not by CGRP. AM at concentrations of 1 pM to 1 nM inhibited CCK-stimulated amylase secretion. AM did not affect CCK binding to acini. In contrast to some other cell types, AM did not affect intracellular cAMP or the rise in Ca^{2+} induced by CCK. Rather, the effect of AM was blocked by pertussis toxin (PTX) suggesting the participation of a PTX sensitive G protein in the action of AM. Additional work on this effect of AM would seem warranted. More recent work on AM in the pancreas has focused on AM produced by pancreatic cancer cells as a mediator of diabetes that often associates with pancreatic cancer, possibly by inhibiting insulin secretion (256).

E. Amylin

Amylin or islet amyloid polypeptide (IAP) was isolated from amyloid rich pancreatic extracts of type 2 diabetic pancreas and shown to be a 37 amino acid peptide that can form oligomers, fibrils and amyloid deposits (44). The amyloid deposits are injurious to the pancreas and are also seen in the brain where they resemble the plaques of Alzheimer's disease (81). Amyloid is a term for protein aggregation state in which the proteins form a β -sheet. The amyloid deposits are injurious to the pancreas and are also seen in the brain of type 2 diabetics (34). Although amylin is not homologous to the Alzheimer $\text{A}\beta$ protein, both can interact with the Amylin receptor which is widely distributed in the brain.

Amylin is produced by islet beta cells, has been localized to the secretory granules (187) and is secreted along with insulin at a ratio of 1:10 to 1:100 (34). Amylin in vivo can inhibit glucagon secretion that occurs at low glucose concentrations

and inhibits glucagon secretion from isolated mouse islets (5). The amylin receptor was identified as a heterodimer of a calcitonin seven transmembrane receptor and a single transmembrane receptor activity modifying protein or RAMP (212). These receptors are widely distributed in the brain. Amylin receptor antagonist increased glucagon secretion (90). The acute effects on insulin secretion are more complex as amylin at low concentrations enhanced insulin release while high concentrations inhibited insulin release from mouse islets (5).

A few reports have evaluated the effect of amylin on the exocrine pancreas. In one report amylin had a small effect to increase basal pancreatic secretion in conscious rats (84). In a study in anesthetized rats, Young et al found no effect on basal secretion but a dose-dependent inhibition of CCK stimulated fluid, amylase and lipase secretion up to 67% (337). This effect was seen at low concentrations of amylin (ED₅₀ was 0.11 μg) comparable to effects reported on gastric emptying. However, multiple studies have shown no effect of amylin on secretion by isolated pancreatic acini or AR42J cells (75, 142, 337). Thus, there does not appear to be a direct effect of amylin on pancreatic exocrine cells and the in vivo effects may be on the CNS. There is also no information available on whether amylin receptors exist in the exocrine pancreas.

F. Pancreastatin

Pancreastatin (PST) was first isolated from pig pancreas as a result of screening for peptides with a C-terminal amide structure and shown to inhibit stimulated insulin release (299). While porcine PST is a 49 amino acid peptide, the biological activity resides in the carboxyl half and requires the C-terminal glycine-amide. PST is believed to be derived from chromogranin A as the result of further processing by prohormone convertase 1. The 52 amino acid sequence predicted by the gene structure of human chromogranin A is homologous to porcine PST and when synthesized the full length peptide and its 29 amino acid carboxy-

terminal had similar activity to porcine PST to inhibit insulin release (85). Subsequent studies confirmed the inhibition of insulin secretion *in vivo*, in the perfused pancreas and in isolated pancreatic islets. For reviews see (267, 315). By immunocytochemistry, pancreastatin was shown to be present in the pituitary, adrenal glands, pancreas and throughout the gastrointestinal tract in cells known to contain chromogranin. In the pancreas, PST colocalizes with all four major endocrine cell types and elsewhere is found in neuroendocrine cells (28, 267). Pancreastatin can be measured in plasma by RIA and may serve as a predictive marker for neuroendocrine tumors where PST is elevated (223, 254).

Along with the inhibition of insulin secretion, multiple natural and synthetic forms of PST (human, porcine, bovine, rat) have been shown to inhibit pancreatic digestive enzyme secretion stimulated by CCK *in vivo* in rats (85, 86, 119) and dogs (55). PST also inhibited pancreatic exocrine secretion stimulated by 2-deoxy-D-Glucose, a central vagal activator (205). By contrast to CCK, pancreatic exocrine secretion stimulated by the cholinergic analog bethanechol *in vivo* was not blocked by PST. Studies of isolated rat pancreatic acini showed no inhibitory action of PST on CCK stimulation (55, 86, 119, 205, 206) although there is one report of inhibition of CCK stimulation in guinea pig acini (128). Because PST inhibited exocrine pancreatic secretion *in vivo* but not on isolated cells, the effect of PST is presumed to be indirect.

One possible site of action is on pancreatic blood flow as shown in anesthetized rats using the hydrogen clearance method (201). These investigators found that caerulein enhanced pancreatic blood flow and this increase was dose dependently inhibited by PST at 100 to 500 pmol/kg per h. However, another study in anesthetized dogs showed no effect of PST at similar concentrations using the laser Doppler flowmeter method although protein and amylase secretion were inhibited (55). The other possible

site is on the neural stimulatory pathway. Herzig et al showed that when pancreatic lobules which contained neural elements were incubated *in vitro*, high K⁺ concentrations stimulated the release of acetylcholine and amylase secretion; both of which were partially inhibited by PST (119). Further studies are necessary to establish pancreastatin as a regulatory peptide and to follow up these potential mechanisms of action. It is also not clear whether PST from a pancreatic or systemic source plays a physiological role in the regulation of exocrine pancreatic function. Absent at present is any information about a PST receptor molecule or PST sensitive ion channel. Moreover, it is not clear what is a physiological concentration of PST. Finally, there is little new information carried out in the last 20 years beyond using PST levels as a tumor marker.

G. Galanin

Galanin is a 29 amino acid peptide isolated from porcine intestine in 1983 and named for its amino terminal glycine and carboxyl terminal alanine (300). It is considered to be a neuropeptide and is found throughout the body with the highest concentrations in the brain, spinal cord and enteric nervous system (11). Galanin is often co-expressed with other peptides or neurotransmitters including norepinephrine, serotonin, GABA and acetylcholine. Galanin acts via 3 major G protein coupled receptors, GalR1, GalR2 and GalR3 (161). In the pancreas, galanin has been localized mainly to nerves present in both the exocrine and endocrine components but also in some studies to islet cells where colocalization with insulin has been observed (9, 62, 180). In dogs, rodents and humans galanin suppresses insulin release both *in vivo* and *in vitro* (161).

A number of studies have evaluated the effect of galanin on isolated rodent acini and the results are presented in the review by Barreto (11). Most show no effect or inhibition. In a study of the isolated, perfused rat pancreas, galanin at low concentrations enhanced both insulin secretion and CCK stimulated amylase secretion (253). On

the other hand, using isolated mouse pancreas lobules, galanin had no effect on carbachol stimulation but inhibited CCK stimulated release suggesting an effect on cholinergic transmitter release (13). Galanin also inhibited acetylcholine release stimulated by veratridine in rat pancreatic

lobules (118). Overall, these studies suggest galanin is more likely to affect the neural control of exocrine secretion rather than directly affecting acinar cells. Galanin could also affect amylase secretion by blocking somatostatin release (11).

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