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Overview of Exocrine Pancreatic Pathobiology

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Abstract

Exocrine pancreas is a source of several enzymes that are essential for the digestive process. The exocrine pancreatic secretion is tightly regulated by the neuroendocrine system. The endocrine pancreas is tightly integrated anatomically and physiologically with the exocrine pancreas and modulates its function. Compound-induced pancreatitis is not a common event in toxicology or drug development but it becomes a significant liability when encountered. Understanding the species-specific differences in physiology is essential to understand the underlying pathobiology of pancreatic disease in animal models and its relevance to human disease. This review will mainly focus on understanding the morphology and physiology of the pancreas, unique islet-exocrine interactions, and pancreatitis.

Keywords

Animal Models; Digestive system; Endocrine system; OTHER

Introduction

Pancreas is not the most common target organ in toxicological studies. However, pancreatitis can be a serious liability in drug development. Understanding the normal morphology and physiology is essential in order to appreciate the pathology of any organ system. In this paper, I will focus on the normal morphology and physiology of exocrine pancreas and the pathogenesis of pancreatitis.

Morphology

The pancreas develops from a common multipotent cell population within the foregut (dorsal and ventral buds) endoderm. The exocrine and endocrine pancreas arise from a common progenitor cell population expressing *Pdx1, Ptf1a* and *Sox9*. These cells in the presence of other factors like *Ngn3, NeuroD, Hnf6* and *Pax4* contribute to the proliferation and differentiation of the endocrine pancreas. The absence of proendocrine factors and transcription factors like *Ptf1a* and *Mist1* leads to the development of exocrine pancreas (Reichert and Rustgi, 2011; Benitez *et al*., 2012). Overall, pathways associated with Hedgehog, Notch and Wnt play critical roles in the development, differentiation and

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proliferation of pancreas. The exocrine pancreas is morphologically mature at birth but attain functional maturity at weaning in most animals (Walthall *et al*., 2005).

There is species-specific variation in the organization of pancreatic tissue. In rabbits, the pancreatic tissue is diffusely distributed through out the mesentery and in primates, dogs and hamsters it is compact. While, in rats and mice it is intermediate since the tail (splenic portion) is relatively compact but the head is dispersed within the duodenal loop's mesentery. The pancreas is the only organ in the body composed of exocrine and endocrine components intermixed within the parenchyma. In rats and mice, the pancreas may be anatomically divided into gastric lobe, duodenal head and tail. The numbers of islets of Langerhans distributed within each of these regions appears to vary by strains. For example, within a 10-week old CD1 mouse on average there are 110 islets in the gastric lobe, 453 islets in the duodenal head and 686 islets in the tail, whereas, in a 10-week old NOD mouse on average there were 120 islets in the gastric lobe, 549 islets in the duodenal head and 489 islets in the tail (El-Gohary *et al*., 2012). The exocrine pancreatic component comprises ~90% of the pancreatic mass and is comprised of acinar, centroacinar and ductal cells; the endocrine component islets of Langerhans comprise about 1-2% and the interstitium with the blood vessels, lymphatics, nerves and fibrous connective tissue stroma comprise the remainder. The pancreas is covered by a thin layer of loose connective tissue that forms septa resulting in the division of the gland into lobules that contain numerous acini. In order to explain the organization of the exocrine pancreatic acini, two models have been proposed. One is the acinar model supported by Takahashi (1984) where the lobules are arranged in grape-like clusters interconnected by ducts and the other is the reticular model supported by Bockman (1976) where the lobules bud off a network of anastomosing tubules (Bockman, 1976; Takahashi, 1984). There are proponents for both the models since they are backed up by data from morphological studies involving retrograde injection of dyes and latex, scanning electron microscopy and 3D reconstruction of serial semithin sections (Motta *et al*., 1997). These models seem to support the morphology across several species and possibly the pathogenesis of some lesions within the exocrine pancreas. For example, the ductular morphology of the tubular complexes as well as the ductular phenotype seen in pancreatic adenocarcinoma seem to support the anastomosing model since in the dimethylbenzanthracene treated rat model, the acinar cells lose their zymogen granules and attain a ductular phenotype and proliferate progressively to form ductular complexes and subsequently an adenocarcinoma with ductular phenotype (Bockman *et al*., 2003). The pancreatic acinus consists of a single layer of pyramidal acinar cells arranged concentrically around a lumen. The narrow apices of the pyramidal cells facing the lumen contain eosinophilic zymogen granules and the broader base of the pyramidal cells is basophilic due to abundant rough endoplasmic reticulum and also contains the nucleus. Each pancreatic acinus is surrounded by a thin basal lamina, scant reticular stroma, and pancreatic stellate cells (similar to the hepatic stellate cells). The quiescent pancreatic stellate cells stain positive for vimentin, desmin, GFAP and Nestin. When activated, these stellate cells express α-smooth muscle actin (Omary *et al*., 2007). The pancreatic stellate cells play important roles in the pathogenesis of chronic pancreatitis and pancreatic cancer. Located centrally within the acinus, the centroacinar cells form an interface between the acinus and the intercalated duct. The intercalated duct continues into intralobular ducts formed by the

ductular cells. The centroacinar cells and the duct cells have carbonic anhydrase and secrete bicarbonate and water that results in the flushing of acinar secretions into the pancreatic ducts. The intralobular ducts fuse to form the interlobular ducts that mainly open into the pancreato-hepatic (biliary) duct or to a lesser extent directly into the duodenal lumen.

The exocrine pancreas is physiologically and morphologically compartmentalized into peri- and tele-insular regions. The peri-insular acinar cells are in the immediate proximity of the islets of Langerhans and are bigger with abundant cytoplasm, larger zymogen granules and larger nuclei than the tele-insular acinar cells that are farther from the islets (Aughsteen and Kataoka, 1993). Due to differences in sizes of the peri- and tele-insular acinar cells, at lower magnification, the islets of Langerhans appear to be surrounded by “halos”. These physiologically normal size differences in the peri- and tele-insular exocrine acinar cells form the so-called “peri-insular halos” (Cosnier, 1955). The difference in the size of peri- and tele-insular acinar cells is greater in mice than in rats, resulting in more prominent peri-insular halos in mice. The peri-insular acinar cells are more resistant (3 hours) to pilocarpine-induced degranulation than the tele-insular acinar cells (1 hour) (Putzke and Said, 1975). The size of peri-insular halos is markedly reduced in alloxan-induced diabetic pancreata compared to control non-diabetic rats. These features of the peri-insular halos are due to the hormones (mainly insulin and possibly other factors) secreted by islets of Langerhans that are locally enriched due to the islet-acinar capillary anastomoses or due to diffusion via the fenestrated capillaries (Wayland, 1997). The peri-insular halos are not recorded in routine toxicity studies but recording any alterations within these halos may provide important information about chemicals affecting islet cells such as alloxan or about chemicals directly affecting the secretions from exocrine pancreas like pilocarpine. Thus, it is important to be cognizant of the heterogeneity of exocrine pancreatic acini during routine toxicologic pathology studies since it may be useful in identifying chemicals that may target the islets of Langerhans (like alloxan) or the exocrine pancreas (like pilocarpine).

Islet-Acinar axis

The rat pancreas is supplied by the splenic, pancreato-duodenal and other minor arteries arising from the celiac or superior mesenteric arteries and drain into the splenic, pancreato-duodenal and other veins into the portal vein. There are about 5000 or more lobules within the rat exocrine pancreas (Murakami and Fujita, 1992). The lobular artery and vein enter the lobules near their base and form lobular capillary plexus and then drain into the lobular veins (Figure 1). The islets of Langerhans comprise ~2% of the pancreas but about 20% of the arterial blood entering the pancreas is supplied to the islets. In a typical rat pancreas, there are about 400 islets that may be located in almost equal numbers either within the exocrine lobules (intralobular) or between tissue spaces along the secretory ducts (interlobular) (Murakami and Fujita, 1992). The intralobular and interlobular afferents arise from lobular and interlobular arteries or their branches, respectively.

Based on their size, the islets receive one or more afferent vessels and give out 3 or more efferent vessels (Figure 1). The intralobular efferents drain either into lobular capillaries or into venous branches in the lobules and the interlobular efferents drain into venous branches in the interlobular spaces or along the secretory ducts. Thus, the islet-acinar axis forms a

direct connection between the islet and lobular capillaries. This islet-acinar portal system has been demonstrated in man, monkey, horse, rabbit, dog, cat, mouse, and rat. However, there are some species differences in this regard. In man (and monkey, pig, cattle, rabbit, dog, cat), most of the islets are intralobular in location and emit only islet-acinar portal vessels and very few islets within the interlobular spaces issue the islet-venous efferent vessels that are continuous with the interlobular veins. In contrast, in rat and mouse, the intralobular vessels drain into both islet-acinar portal vessels and intralobular veins and the interlobular arteries drain into the interlobular veins (Murakami *et al*., 1993).

In the rat, the afferent arteries supplying the islets are first divided in the peripheral zone of the islet and then break into several capillaries resulting in a glomerular meshwork that penetrates the islets and converge to form the efferent supply that passes through the surrounding exocrine acini before joining the venous drainage. The vascular plexus within the islets is about 5 times denser than the acinar lobular plexus (Henderson and Moss, 1985). The capillary network in islets has about ten times more fenestrae than capillaries of the exocrine tissue (Henderson and Moss, 1985). This unique anatomic arrangement of the islet-acinar portal system facilitates the interaction of several proteins secreted by the islets with the surrounding exocrine tissue.

Influence of the islet-acinar axis on exocrine function

The islets of Langerhans are distributed within the exocrine pancreas and this arrangement serves an important physiological function since several islet-derived hormones and peptides directly influence the exocrine function. In addition to these peptides and islet-derived hormones, neurotransmitters like acetylcholine and norepinephrine, play an important role in the exocrine pancreatic homeostasis. Several unique cell types within the islets secrete corresponding hormones and peptides for influencing exocrine function. The alpha (α) cells secrete glucagon, the beta (β) cells produce insulin and amylin, the delta (δ) cells produce somatostatin (SST), the epsilon (ε) cells produce ghrelin, and the PP or F cells produce pancreatic polypeptide and adrenomedullin. In addition, islets also contain several neuropeptides/cotransmitters that modulate exocrine pancreatic function. The stimulatory neuropeptides/cotransmitters include pituitary adenylate cyclase-activating peptide (PACAP), and nitric oxide (NO), vasoactive intestinal peptide (VIP), and Angiotensin II. The inhibitory factors for exocrine pancreatic secretion include SST, pancreatic polypeptide, ghrelin, pancreastatin, adrenomedullin, galanin, calcitonin gene-related peptide (CGRP), neuropeptide Y (NPY), and peptide YY (PYY) (Barreto *et al*., 2010).

Insulin is one of the major islet hormones and the most well characterized regulator of exocrine pancreatic function. Insulin positively influences pancreatic growth and exocrine function. Insulin binds to its own receptor on the acinar cells to stimulate and potentiate amylase secretion (Mossner *et al*., 1985). In addition, it also potentiates secretagogue-stimulated secretion of amylase. The role of glucagon on exocrine function is not clear due to contradictory data (Barreto *et al*., 2010). *Pituitary adenylate cyclase-activating peptide* (PACAP) has a direct stimulatory effect on the exocrine pancreatic secretion as well as flow rate without affecting the secretin and VIP levels (Alonso *et al*., 1994). This stimulatory effect of PACAP is mediated by a cholinergic mechanism and it has a synergistic effect with

CCK (Naruse *et al*., 1992; Kitagawa *et al*., 1995). NO exerts a stimulatory effect of exocrine pancreatic secretion probably via the generation of cyclic guanosine monophosphate and the release of endogenous neurotransmitter in the pancreas (Ember *et al*., 2001; Yago *et al*., 2001). *Vasoactive intestinal peptide* (VIP) shares structural similarity with secretin as well as glucagon. It has a stimulatory action on exocrine pancreatic secretion, especially with the increasing pancreatic secretion flow rate and secretin levels, suggesting that these effects are likely secondary to its effect on secretin levels (Alonso *et al*., 1994). The pancreas contains a local renin-angiotensin system and the angiotensin II receptors AT1 and AT2 are expressed in pancreatic acinar cells, ducts, islets and blood vessels (Leung and Carlsson, 2001; Tsang *et al*., 2004). Angiotensin II stimulates exocrine pancreatic secretion (Tsang *et al*., 2004) but inhibits the synthesis and release of insulin from the islets (Lau *et al*., 2004).

Somatostatin (SST) acts as a hormone and as a neurotransmitter. It acts as a hormone by inhibiting CCK or cerulein stimulated amylase secretion and inhibits insulin secretion. SST binds to its own receptor on the acinar cells and reduces intracellular cyclic AMP and subsequent Ca^{2+} signaling (Ohnishi *et al*., 1994). SST acts as a neurotransmitter by modulating vagal and sympathetic pathways or via the SST receptor 2 in the dorsal vagal complex (DVC). In addition, it can indirectly inhibit pancreatic secretion via the intrapancreatic cholinergic mechanism by inhibiting acetylcholine release in the peripheral nerve terminals (Heintges *et al*., 1994). *Pancreatic polypeptide* inhibits exocrine pancreatic secretion during both the interdigestive and postprandial states. It has been demonstrated to inhibit CCK-stimulated release of amylase and by inhibiting the stimulatory effect of insulin on amylase secretion (Louie *et al*., 1985). *Ghrelin* inhibits exocrine pancreatic secretion but its precise mechanism of action is not known but is thought to be via intrapancreatic neurons (Zhang *et al*., 2001) or by inhibiting insulin secretion (Tong *et al*., 2010). *Pancreastatin* inhibits glucose induced insulin secretion (Tatemoto *et al*., 1986). In addition, it also inhibits exocrine secretion irrespective of the stimulus used and this is probably mediated by modulation of presynaptic acetylcholine release (Herzig *et al*., 1992) and/or reduction of local pancreatic blood flow (Migita *et al*., 1999). *Adrenomedullin* colocalizes with pancreatic polypeptide in the PP or F cells and inhibits insulin secretion (Martinez *et al*., 1996). *Galanin* inhibits the secretion of insulin (McDonald *et al*., 1985) and somatostatin (Amiranoff *et al*., 1990). Its effect on amylase secretion is dependent on the stimulus, i.e. it inhibited amylase secretion stimulated by cerulein at physiological concentrations but it had no effect on carbachol-stimulated amylase secretion (Barreto *et al*., 2009). The cerulein-induced stimulation of amylase secretion is secondary to inhibition of insulin secretion and inhibition of postganglionic cholinergic nerves (Barreto *et al*., 2010). This indicates the close influence of endocrine pancreas on exocrine pancreatic secretion. *Calcitonin gene-related peptide* (CGRP)–immunoreactive neurons within the pancreas may play a role in influencing exocrine secretion. CGRP inhibits exocrine secretions indirectly by stimulation and release of SST into systemic circulation (Mulholland *et al*., 1989) and by sympathetic noradrenergic efferent nerves via α-adrenergic receptor (Messmer *et al*., 1993). *Neuropeptide Y* (NPY) dose dependently inhibits CCK-stimulated exocrine pancreatic secretion but does not alter bicarbonate concentration in secretin-stimulated pancreatic secretions (Mulholland *et al*., 1991). The action of NPY on pancreatic exocrine secretions is likely indirect via alteration of intrapancreatic neurotransmission (Mulholland *et al*., 1991)

or via its splanchnic vasoconstrictive effect (Sumi *et al*., 1991). *Peptide YY* (PYY) is structurally similar to pancreatic polypeptide and significantly inhibits secretin- and CCK-stimulated pancreatic exocrine secretion (Tatemoto, 1982). PYY acts via intrapancreatic cholinergic nerves and is independent of adrenergic nerves or extrapancreatic nerves (DeMar *et al*., 1991; Brodish *et al*., 1993; Brodish *et al*., 1995). Peptide YY acts via the Y1 receptor in rats and Y2 receptor in dogs (Grandt *et al*., 1995; Teyssen *et al*., 1996). *Substance P* binds to neurokinin receptors on acinar cells and modulates pancreatic neural signaling, and blood flow that subsequently influence exocrine pancreatic secretion (Barreto *et al*., 2010).

Physiology of exocrine pancreatic secretion

The function of the exocrine pancreas is tightly regulated by the neuroendocrine system. Please refer to the excellent reviews on the topic for more details (Konturek *et al*., 2003a; Owyang and Logsdon, 2004; Wang and Cui, 2007; Owyang, 2009; Singer and Niebergall-Roth, 2009)

The exocrine pancreatic secretions are elicited via a complex interplay of neural, humoral and paracrine mediators (Figure 2). The islets and the exocrine tissue are richly innervated with central and autonomic nervous system with afferent and efferent signaling. The vagus nerve serves a major role in the regulatory pathway. In addition, enteropancreatic neurons between the pancreas and the gastrointestinal tract mediate the vago-vagal enteropancreatic reflexes that are important in the intestinal phase of the exocrine pancreatic secretion. The vago-vagal enteropancreatic reflex consists of the afferent and efferent fibers of the vagus nerve that coordinate responses to the gut stimuli via the dorsal vagal complex. The intrapancreatic postganglionic neurons are activated by efferents arising from the duodenal mucosa that is in contact with chyme (intestinal phase). Acetylcholine released by these neurons act on the M1 and M3 muscarinic receptors on the acinar cells to elicit exocrine secretions (Singer and Niebergall-Roth, 2009).

Besides cholinergic nerves, the peptide cholecystokinin (CCK) is a very important mediator of exocrine pancreatic secretory activity and also has a trophic effect on pancreas (Yamamoto *et al*., 2003). CCK is a heterogenous protein secreted by I cells in the small intestine and by neurons in the brain. The plasma CCK that originates from the small intestine is a mixture of several types of CCKs (CCK-58, 33, 22, 8) but the prominent molecular forms in the blood are different in different species, i.e. CCK-58 in rats and dogs; CCK-33 in humans, and CCK-22 in pigs (Eysselein *et al*., 1987; Cantor and Rehfeld, 1989; Rehfeld *et al*., 2001; Reeve *et al*., 2003; Wang and Cui, 2007). CCK, in addition, also inhibits gastric emptying, gastric acid secretion, and gall bladder contraction. Since physiological levels of CCK stimulate exocrine pancreatic secretion in humans and rodents, it was assumed that CCK stimulates CCK-A receptor. However, exocrine pancreatic secretion by physiological levels of CCK (but not supraphysiological levels) is inhibited completely by atropine suggests the importance of cholinergic stimulation in eliciting exocrine secretion (Konturek *et al*., 2003b). In addition, human pancreatic acini do not have any functional CCK receptors and are not responsive to physiological concentrations of CCK in vitro (Ji *et al*., 2001; Miyasaka *et al*., 2002). In contrast, rodent pancreatic acini are

responsive to physiological concentrations of CCK in vitro owing to the presence of CCK-A receptors on the pancreatic acini. Thus, it is generally accepted that in humans exocrine pancreatic secretion is almost exclusively mediated through the cholinergic stimulation of the acini where as in rodents, there is a dual mechanism of stimulation, both direct CCK-A receptor stimulation as well as indirectly via the cholinergic stimulation (Owyang, 2009).

Independent of the action of CCK, the intestinal serotonin also mediates exocrine pancreatic secretion. Luminal factors such as osmolarity and disaccharides activate 5-HT3 receptors, whereas mechanical stimulation activates both 5-HT3 and 5-HT2 receptors on mucosal vagal afferent fibers in the intestine (Li *et al*., 2001). Activation of these serotonin receptors stimulates exocrine pancreatic secretion. The enterochromaffin cells within the intestinal mucosa are the richest source of serotonin in the gut. Serotonin may act as a paracrine substance and mediate exocrine pancreatic secretion via a cholinergic pathway similar to that of CCK since acute vagotomy, and perivagal or luminal application of capsaicin abolishes serotonin-induced pancreatic secretion (Zhu *et al*., 2001). CCK and serotonin may act at the level of the nodose ganglia to synergistically increase exocrine pancreatic secretion and this is exemplified by the robust postprandial exocrine pancreatic secretion mediated by modest increases in plasma CCK levels (Owyang and Logsdon, 2004).

Secretin is another major hormone that influences exocrine pancreatic secretion. It plays an important role in the secretion of bicarbonate rich fluid that helps in flushing the pancreatic zymogens from the acinar lumen into the pancreatic ducts. In addition, secretin plays inhibitory roles in gastric acid secretion, and gastric motility. Luminal acid influenced release of secretin is mediated by a secretin releasing peptide that in turn is dependent on vagal afferent pathways. Secretin's action at physiological doses is abolished by atropine. Thus, similar to CCK, secretin's actions are also mediated by vagal afferent cholinergic pathways (Li *et al*., 1990). Similar to serotonin, CCK and secretin also acts at the level of the nodose ganglia to synergistically increase exocrine pancreatic secretion (Owyang, 2009).

Drug-induced pancreatitis

Pancreatitis in humans may be manifested as a pain in the upper abdomen radiating to the back, and nausea that aggravates with eating. It can be mild or fulminant with severe systemic effects. In general human population, the incidence of pancreatitis is about 2% but in certain cohorts like the HIV patients, the incidence can be up to 40% (Trivedi and Pitchumoni, 2005). The principal causes of pancreatitis in humans include alcoholism and biliary obstruction. However the etiology of pancreatitis may be divided into several categories, such as, toxic (alcoholism, pesticides, and drugs); obstructive (gallstones, tumors, worms and congenital defects); metabolic (hyperlipidemia, hypercalcemia and acidosis); infectious (parasitic, viral and bacterial) and genetic (Cystic fibrosis transmembrane conductance regulator (CFTR), Pancreatic secretory trypsin inhibitor (PSTI1), Serine protease inhibitor Kazal-type 1 (SPINK1), Cationic trypsinogen1 (PRSS1)). The index of suspicion of drug-induced pancreatitis is very low especially when compared to drug-induced liver injury due to the subclinical nature of early pancreatitis and the absence of pancreatic enzyme evaluation in routine clinical pathology. As a result, it is under-diagnosed and under-reported. Even when it is suspected, it is difficult to establish a

link between pancreatitis and the suspect drug due to the long latency of onset of the disease. In addition, even if pancreatitis is diagnosed, usually alcohol or biliary diseases are implicated and the drug remains a silent actor and is never a suspect (Trivedi and Pitchumoni, 2005). There have been several surveys aimed at identifying drugs associated with pancreatitis and several algorithms have been proposed (Mallory and Kern, 1980; Trivedi and Pitchumoni, 2005; Badalov *et al*., 2007). In these surveys, several categories of drugs have been implicated to be associated with pancreatitis, such as antimicrobials (pentavalent antimonials, tetracycline, pentamidine, trimethoprim/sulfamethoxazole, sulfasalazine); HIV drugs (didanosine, nefilnavir); Diuretics (furosemide); GI and pancreatobiliary (azathioprine, 6-mercaptopurine, mesalamine); Immunosuppressive (L-asparaginase, dexamethasone) and Nervous system (valproic acid, opiates). The mechanism of action of these drug-induced pancreatitis is not really well addressed since most of these drugs are not direct pancreatic toxicants but are “associated” with other etiological factors or idiosyncratic factors that result in pancreatitis in a temporal and context dependent manner. Compared to the liver, the pancreas has a respectable complement of xenobiotic metabolizing enzymes and the distribution of these enzymes within the pancreatic parenchyma varies greatly depending on the cell type. In all the species examined, the endocrine pancreas had the greatest amount of the phase I and II metabolizing enzymes compared to the exocrine pancreas and it is not surprising that the endocrine pancreas is more often a target of pancreatic toxicity than exocrine pancreas (Ulrich *et al*., 2002). There are very few studies that examined metabolism of drugs and chemicals within the pancreatic tissue and as a result only a few xenobiotics (Cyanohydroxybutene, 2,3,7,8-tetrachlorodibenzo-p-dioxin, L-arginine, tacrolimus, organophosphates) can be definitely identified as pancreatic toxicants (Nalesnik *et al*., 1987; Tani *et al*., 1990; Longnecker, 2002; Yoshizawa *et al*., 2005; Walgren *et al*., 2007; Singh *et al*., 2007).

Even though supramaximal stimulation of pancreas is not a common cause of pancreatitis in humans, secretagogue hyperstimulation models such as cerulein-induced hyperstimulation with or without sensitizers like ethanol and LPS are used to understand the pathophysiology of pancreatitis (Lerch and Gorelick, 2013). The cerulein hyperstimulation model is most widely used because of its ease of induction, non-invasiveness, and reproducibility. The pathogenesis of secretagogue-induced pancreatitis has been reviewed in several recent papers (Saluja *et al*., 2007; Van Acker *et al*., 2007; Lerch and Gorelick, 2013). Several factors have been implicated in the pathogenesis of secretagogue-induced pancreatitis. A detailed review is beyond the scope of this paper. For more information on the pathogenesis of secretagogue-induced pancreatitis, please refer to the following reviews (Saluja *et al*., 2007; Van Acker *et al*., 2007; Lerch and Gorelick, 2013). Briefly, at supramaximal doses the pancreatic enzyme secretion is blocked resulting in colocalization of zymogens and lysosomes, activation of trypsinogen by cathepsin B and subsequent activation of other zymogens by trypsin, the resulting acinar cell injury and release of chemokines and cyokines causes inflammation and infiltration of leukocytes. The leukocytes secrete more cytokines and potentiate a self-propagating inflammatory reaction and systemic disease (Saluja *et al*., 2007).

The CCK-A receptors in the rat pancreas exist in both high- and low-affinity states and these contribute to some understanding of the pathogenesis of secretagogue-induced pancreatitis. CCK and its agonists cerulein or carbachol have a biphasic or bell shaped dose response curves, i.e. at physiological dose stimulation there is an increase in amylase secretion, but at high (supramaximal) doses, the secretion of amylase is inhibited. In addition at supramaximal stimulation, pancreatitis is observed. A novel CCK agonist CCK-JMV-180 has a unique monophasic dose response curve compared to CCK and its agonists in that, its stimulation curve is more or less a plateau at both low and high doses (Saluja *et al*., 1989). This indicates that exocrine pancreatic secretion at physiological doses of CCK and its agonists as well as CCK-JMV-180 is mediated by high-affinity receptors. In contrast, the inhibition of exocrine secretion and induction of pancreatitis at high doses of CCK and its agonists is mediated by low-affinity receptors. CCK-JMV-180 acts as an antagonist of the low affinity receptors and prevents the inhibition of pancreatic exocrine secretion and also pancreatitis. Thus, the inhibition of enzyme secretion at high doses via the low affinity receptors plays an important role in secretagogue-induced pancreatitis (Saluja *et al*., 2007).

Calcium signaling plays an important role in the molecular pathways of several metabolic cells. CCK and its agonists bind to G-protein coupled transmembrane receptors on the basolateral surface of the pancreatic acinar cells and activate phospholipase C resulting in the cleavage of phosphatidylinositol-4,5-bisphosphate (PIP2) into diacylglycerol (DAG) and inositol 1,4,5-triphosphate (IP3). IP3 causes the release of Ca^{2+} from the endoplasmic reticulum (Thorn *et al*., 1993a; Thorn *et al*., 1993b). Based on the type of stimulation, the duration of the intracellular Ca^{2+} oscillations or spikes can vary. These Ca^{2+} spikes result in a burst of exocytic activity causing the release of zymogens. With acetylcholine, these spikes are restricted to the secretary pole of the cell where as, with CCK, the spikes are local followed by distribution to the entire cell. With physiological stimulation, the zymogens are released only from the secretory pole where as, with supramaximal stimulation, there is a sustained increase in Ca^{2+} spikes resulting in a significant increase in zymogen release followed by sustained increase at lower level (Matozaki *et al*., 1990; Thorn and Petersen, 1993). Hypercalcemia has also been associated with pancreatitis and increased serum calcium sensitizes the exocrine pancreas to secretogogue-induced pancreatitis (Mithofer *et al*., 1995a; Mithofer *et al*., 1995b; Frick *et al*., 1995). Hypocalcemia observed during pancreatitis is usually a sequela of pancreatitis and is likely related to precipitation and sequestration of calcium in soft tissues, and alterations in calcitonin and parathyroid hormone (Edmondson, 1952; Norberg *et al*., 1975; Bhattacharya *et al*., 1985; Izquierdo *et al*., 1985).

The subapical actin cytoskeleton is important for the secretion of zymogens after appropriate stimulation of the acinar cells. During supramaximal stimulation, the actin cytoskeleton and the associated intermediate filaments are ablated resulting in the prevention of apical exocytosis. However, treatment with CCK-JMV-180 prevents this process suggesting that the low affinity receptors may play a role in this process (O'Konski and Pandol, 1993). Once the zymogen granules are not secreted, they accumulate within the acinar cell. Upon excess stimulation, these accumulated zymogen granules colocalize with lysosomal enzymes like cathepsin B (Watanabe *et al*., 1984; Saito *et al*., 1987; Saluja *et al*., 1987) and convert the

inactive trypsinogen into trypsin, which in turn activates a host of other peptidases, nucleases, lipases and hydrolases. The activation of these enzymes results in hyperamylasemia, hyperlipasemia, pancreatic edema, acinar cell degeneration and necrosis.

Supramaximal stimulation by CCK results in a powerful, biphasic activation of NF-κB (Gukovsky *et al*., 1998). This activation of NF-κB was not noted during pancreatic stimulation with physiological levels of CCK or with JMV-CCK-180. In addition, JMV-CCK-180 is able to abolish cerulein-induced NF-κB activation (Gukovsky *et al*., 1998). NF-κB transcriptionally regulates the expression of IL6 and IL8 that recruit inflammatory cells to the site of hyperstimulation (Zaninovic *et al*., 2000). The recruited inflammatory cells secrete more inflammatory cytokine mediators such as TNF-α, IL1, IL2, IL6, IL8 and platelet activating factor (PAF) as well as anti-inflammatory cytokines such as IL10 and IL1R antagonist resulting in systemic inflammation and sepsis (Makhija and Kingsnorth, 2002).

In summary, a thorough understanding of unique histological features and physiology of exocrine pancreas is essential in order to better understand the pathophysiology of pancreatitis. Inspite of the substantial strides made in understanding the pathophysiology of pancreatitis, it still remains a significant clinical problem mainly due to the myriad factors that are associated with the pathogenesis and diagnosis of pancreatitis.

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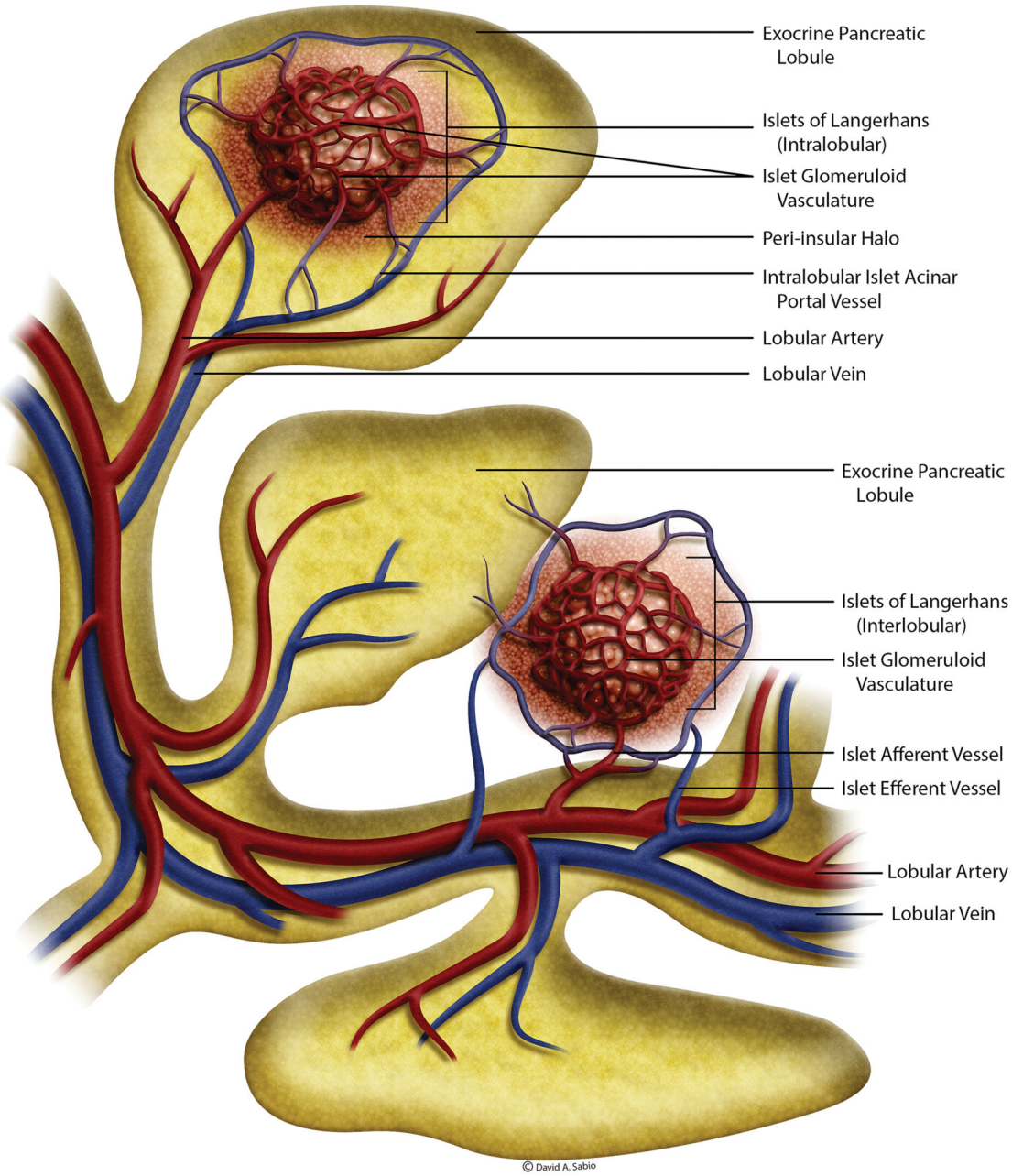

Figure 1.

An artist's rendering of the vasculature within the rat pancreas. The islets and acini have a tightly integrated blood supply. The islets may be located intralobular or interlobular and have corresponding blood supply. The blood draining from the intralobular islets pass through the exocrine acini before joining the venous system. The peptides from the islets contributes to the regulation of peri-islet acini (please see text for more details). (Adapted from Murakami and Fujita, 1992)

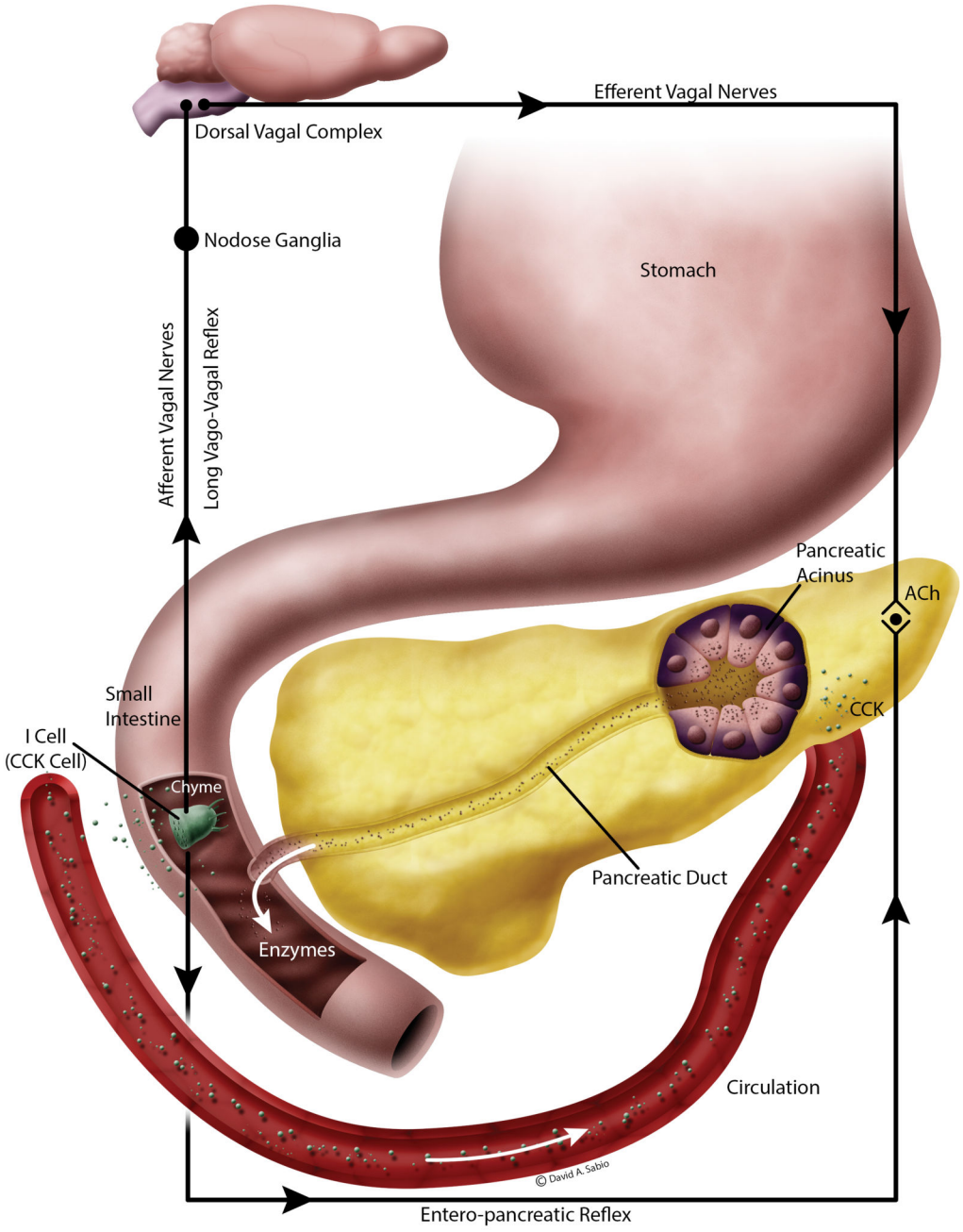

Figure 2.

Cholecystokinin (CCK) stimulation of the exocrine pancreas is species dependent. In rodents, CCK released from the I cells within the intestine enter the circulation and directly stimulate the CCK1 receptors on the exocrine acini to stimulate secretions. In addition, CCK can also activate the sensory nerve fibers resulting in the activation of long vago-vagal and short enteropancreatic cholinergic reflexes. However, in humans, the latter process is the

most accepted physiological process of exocrine stimulation. (Adapted from Wang and Cui, 2007)