Chapter 4
Pancreatic Physiology

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1 Introduction to the Pancreatic Functions

The human **pancreas** consists of **two organs in one structure**: the **exocrine gland** made up of ***pancreatic acinar cells*** and ***duct cells*** that produce digestive enzymes and sodium bicarbonate, respectively; the **endocrine gland** made up of ***four islet cells***, namely *alpha-, beta-, delta-, PP-,* and *ipsilon- cells* that produce glucagon, insulin, somatostatin, pancreatic polypeptide, and ghrelin respectively. While the physiological role of **exocrine pancreas** (>80 % by volume) is to secrete digestive enzymes responsible for our normal digestion, absorption and assimilation of nutrients, the **endocrine pancreas** (<2 % by volume) is to secrete islet peptide hormones for the maintenance of our glucose homeostasis. The pancreatic functions are finely regulated by neurocrine, endocrine, paracrine and/or intracrine mechanisms. Thus, dysregulation of these pathways should have significant impacts on our health and disease. Nevertheless, the underlying mechanisms by which pancreatic functions are regulated remain poorly understood.

Embryologically, the human pancreas originates from **two separate outgrowths**, designated as the ***dorsal*** and ***ventral*** buds, from the foregut endoderm directly posterior to the stomach; it is similar to the pancreas development in murine. The **dorsal bud** arises from evagination of the dorsal side of the primitive duodenum at around 3.75th week of gestation while the **ventral bud** arises from the base of the hepatic diverticulum at around 4.5th week of gestation. After undergoing the rotation of the ventral bud to the right of and then behind the developing

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duodenal loop, the dorsal and ventral buds come into contact with one another and fusion of the two buds occurs at the end of 6th week of gestation. The ventral bud gives rise to the head and uncinate process of the pancreas while the dorsal bud forms the remaining portion of the organ. Meanwhile, the ventral bud duct is also fused with the distal portion of the dorsal bud duct and thus forms the subsequent **duct of Wirsung**, the main pancreatic duct which runs through the entire pancreas. The proximal portion of the dorsal bud duct becomes the future **duct of Santorini**, the accessory duct. During the fusion of the two pancreatic buds at 6th–7th week of gestation, the pancreatic architecture is observed with tubular structures surrounded by dense mesenchymal tissues next to the duodenal structure. The **mesenchymal layer** probably provides signals to the invading epithelium that regulates the balanced development of the future endocrine and exocrine portions of the pancreas. The dual origin of the organ accounts for the regional differences in the islet cell distribution in adult pancreas. In addition, the **arterial blood supply** of the pancreas arises from branches of the *splenic, gastroduodenal* and *superior mesenteric arteries*. **Extrinsic neural innervation** comes from both parasympathetic and sympathetic fibers through the splenic subdivisions of the celiac plexus. These nerves innervate all the major components of the pancreas, including blood vessels, pancreatic acinar cells, and duct and islet cells.

2 Digestive Enzyme Secretion of the Exocrine Pancreas

2.1 Synthesis and Exocytosis of Protein by the Pancreas

Acinus as the Functional Unit of Exocrine Pancreas

The major functional unit of the exocrine pancreas is the **acinus** or acini (in pleural), composed of contiguous, pyramid-shaped glandular cells with their apex facing the lumen of the acinus (Fig. 4.1). These cells have many noteworthy specialized features. First, they are **highly polarized**, having distinct functional and structural differences in the apical and basolateral plasma-membrane domains. Second, acinar cells have **well developed Golgi and rough endoplasmic reticulum complexes**, essential for the synthesis and storage of secretory proteins. **Zymogen or storage granules** can be also found in the apical (luminal side) cytoplasm of the cell, and they vary in number depending on the stage of development and state of stimulation by neuronal and hormonal agents. **Nuclei** are located at the very *base* of the cell.

Mechanism of Protein Secretion by the Acinus

The primary function of the pancreatic acinar cell is to produce large amounts of digestive enzyme proteins that are eventually transported through the ductal system into the duodenum to be mixed with intestinal chyme. The cellular events

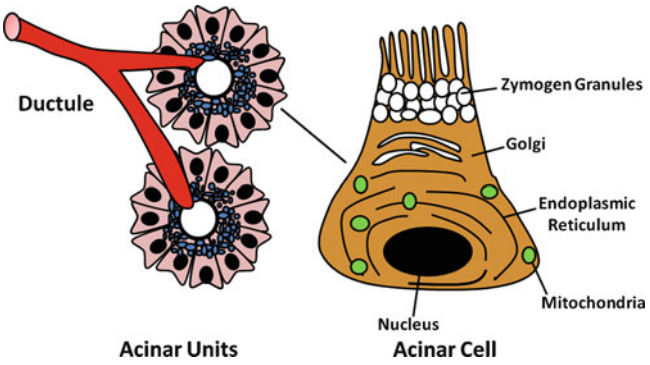

Fig. 4.1 A schematic diagram showing the structure and functional unit of the exocrine pancreas. The acinus is the functional unit of the exocrine pancreas, which is composed of contiguous pyramid-shaped glandular cells with their apex toward the lumen of the acinus. Acinar cells have well-developed Golgi and rough endoplasmic reticulum complexes, essential for synthesizing and storing large amounts of secretory proteins. Zymogens or storage granules can be found in the apical or luminal side of the cell

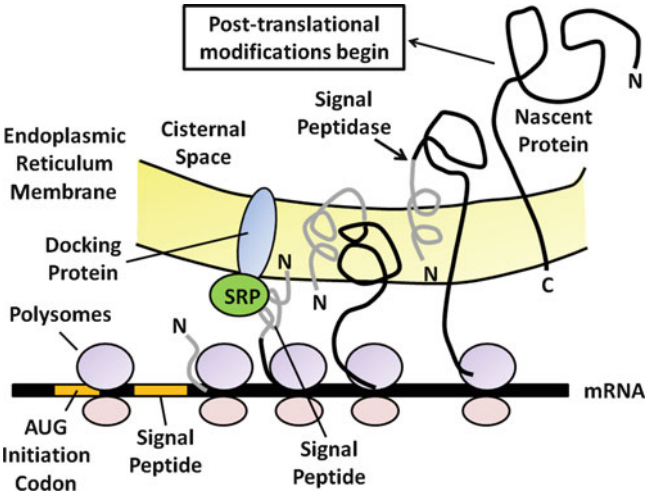

Fig. 4.2 The processing and synthesis of pancreatic digestive enzymes. Proteins for export are first synthesized on polysomes attached to the outer or cytosolic aspect of the rough endoplasmic reticulum at the base of the acinar cell. As translation continues, the nascent protein transverses the endoplasmic reticulum membrane and enters the cisternal space

involved in the synthesis and export of these proteins have been well-characterized. Proteins for export are synthesized on polysomes attached to the outer or cytosolic aspect of the rough endoplasmic reticulum located at the base of the acinar cell. A special signal sequence after the AUG initiation codon is translated into an amino-terminal extension called the **signal peptide** (Fig. 4.2). The signal peptide is avidly

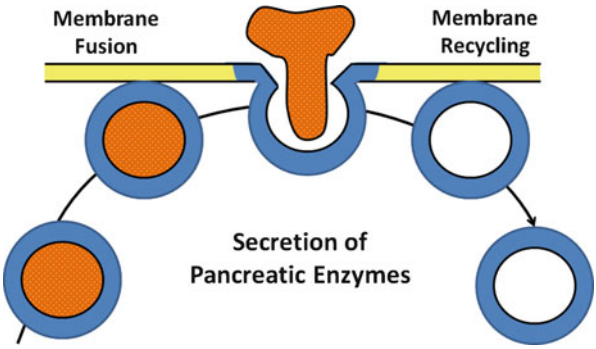

Fig. 4.3 The process of exocytosis of pancreatic enzyme secretion. After an appropriate neural or hormonal stimulus, zymogen granules move to apical membrane, fuse with plasma membrane, and discharge their contents into the luminal space by the process of exocytosis

bound by a cytosolic protein called the **signal-peptide recognition particle** (**SRP**), which facilitates the binding of the mRNA-ribosomal complex to the endoplasmic reticulum (ER) membrane. It does so by recognizing and binding to a specific ER-membrane receptor or docking protein. Because of the hydrophobicity of the signal peptide, it enters the internal ER compartment. As translation continues, the rest of the protein traverses the ER membrane and enters the cisternal space. The signal peptide is then cleaved off by an enzyme called **signal peptidase**. The nascent protein then undergoes several post-translational modifications, including the formation of disulfide bridges, glycosylation, sulfation, and phosphorylation. Post-translational processing of secreting proteins is important in folding them into proper tertiary and quaternary configurations. Within 20–30 min of their synthesis, these proteins are transferred to the Golgi complex, where additional processing of the secretory proteins takes place. These modifications generally involve the removal of mannose groups from glycoproteins and progressive buildup to a complex glycosylated form by sequential additions of monosaccharides. These glycoproteins move from the cis to trans side of the Golgi complex and are eventually concentrated and packaged into storage granules. The secretory granules then move by an undefined mechanism to the apical portion of the acinar cell. Upon an appropriate neural of hormonal stimulus, zymogen granules move to the apical membrane, fuse with the plasma membrane, and discharge their contents into the luminal space by the process of exocytosis (Fig. 4.3).

Regulation of Digestive Enzyme Secretion

Several intracellular messengers appear to play a role in regulating the secretion of digestive enzymes. Increases in intracellular calcium are stimulated by agents such as *cholecytokinin (CCK), acetylcholine, bombesin* (gastrin-releasing peptide or GRP is the mammalian equivalent), and *substance P*. Although receptors on acinar cells for all these agents have been identified, it is likely that **cholinergic muscarinic receptors** are the major pathway for regulation (discussed below). These agents

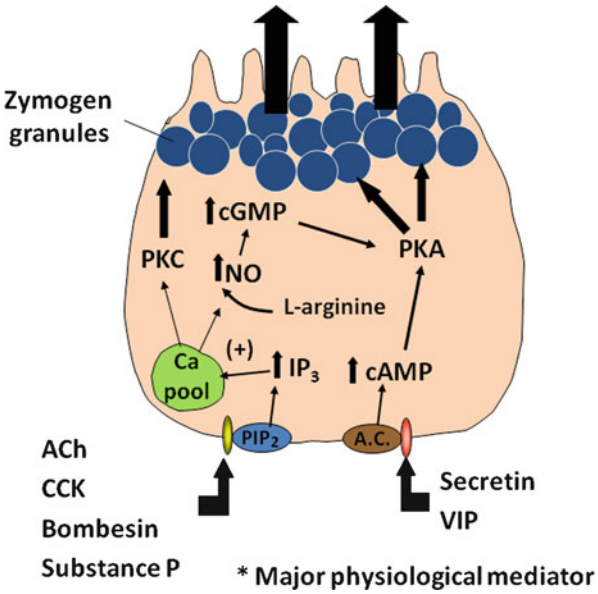

Fig. 4.4 A cellular model showing the regulation of protein secretion by a pancreatic acinar cell. Upon stimulation by agonists such as cholecystokinin (CCK), secretin, vasoactive intestinal peptide (VIP), and acetylcholine (ACh), signal transduction pathways are evoked in the pancreatic acinar cell. ACh and CCK stimulate acinar cell secretion by activating inositol triphosphate (IP_3)/diacyl glycerol (DAG) signaling pathways, thus leading to increased cytosolic Ca^{2+} and protein kinase C (PKC). Secretin and VIP stimulate secretion by elevating intracellular cAMP, thereby activating protein kinase A (PKA)

stimulate phosphatidylinositol (PI) metabolism, leading to the formation of inositol 1,4,5-triphosphate (IP_3) and 1,2-diacylglycerol (DAG) (Fig. 4.4). IP_3 activates IP_3 receptors of calcium storage organelles, releasing Ca^{2+} and increasing cytosolic Ca^{2+}. Though being transient, this stimulation serves to trigger a number of more sustained biochemical and functional events. Increased Ca^{2+} activates calcium-dependent, constitutively expressed **nitric oxide synthase** (**NOS**), which produces nitric oxide (NO) from L-arginine. The activity of this enzyme also appears to be sensitive to the level of intracellular calcium stores, as depletion of these stores can independently activate NOS activity. NO then appears to stimulate soluble guanylate cyclase activity to increase cellular cyclic guanosine monophosphate (cGMP) levels. cGMP stimulates increased plasma-membrane permeability to Ca^{2+} to sustain increased cytosolic Ca^{2+}, possibly through activation of a cGMP-dependent cation channel or through the action of cGMP-dependent protein kinases. Increases in cytosolic Ca^{2+} stimulate exocytosis of zymogen granules, probably through calcium-calmodulin-dependent protein kinases. The **activation of protein kinase C** by DAG may also play a role in stimulating acinar cell secretion, particularly in sustaining the effect after receptor activation.

Synchronization of Secretory Responses

Recently, the role of **intercellular gap junctions** in "synchronizing" acinar cells of a functional unit has become evident. Gap junctions provide points of low electrical resistance and for intercellular permeation by small-charge molecules such as IP_3 or Ca^{2+}. Local application of agonists to one region of an acinar unit, for example, stimulates a regional increase in cellular Ca^{2+}. However, the activation of other cells of the unit soon becomes apparent, most likely through the propagation of an activating signal via gap junctions. Physiologically, this **intercellular coupling mechanism** provides an effective way to produce a unified secretory response by the acinar unit.

The relative importance of the above Ca^{2+}-dependent agents for the physiological regulation of pancreatic functions is not entirely clear (see discussion at greater length later in the chapter). Experimentally, these agents do appear to have different effects on acinar cell function, even though they all appear to activate PI metabolism. This could be attributed to differences in their effects on PI metabolism or on receptor coupling with other transduction pathways. For instance, *acetylcholine* and *CCK* vigorously stimulate IP_3 and DAG, the latter eventually desensitizing both receptors. *Bombesin*, on the other hand, has far less effect on DAG formation and does not cross-desensitize receptor activation by CCK or acetylcholine. As another example, *CCK*, but not acetylcholine, has trophic effect on pancreatic acinar cells. This may arise from CCK-receptor coupling with the phospholipase D pathway, which causes the formation of phosphatidic acid and choline, important for mediating CCK trophism.

Agents such as *secretin* and *vasoactive intestinal peptide (VIP)* also stimulate acinar cell secretion, apparently through the activation of adenylate cyclase and increased cyclic adenosine monophosphate (cAMP). Although the exact mechanisms that result in enzyme secretion are not well understood, cAMP-dependent protein kinases are probably involved. The physiological role of cAMP-mediated agonists in regulating acinar cell functions is also not well characterized, although it is believed to be less important than calcium-mediated agonists. However, these agents do appear to augment or potentiate the actions of Ca^{2+}-mediated agonists (Discussion below).

Finally, it should be noted that **microtubules** or **microfilaments** of the **actin-myosin system** play an important role in the movement of secretory granules to the site of exocytosis. For example, *cytochalasin B,* an *inhibitor of the microfilament system*, inhibits the exocytic process. After discharge of the contents of the zymogen granules, excess membrane can be retrieved by the cell and reutilized. Several lines of evidence suggest that this reutilization process involves endocytosis and relocation of these internalized membranes to the trans side of the Golgi complex and to lysosomes.

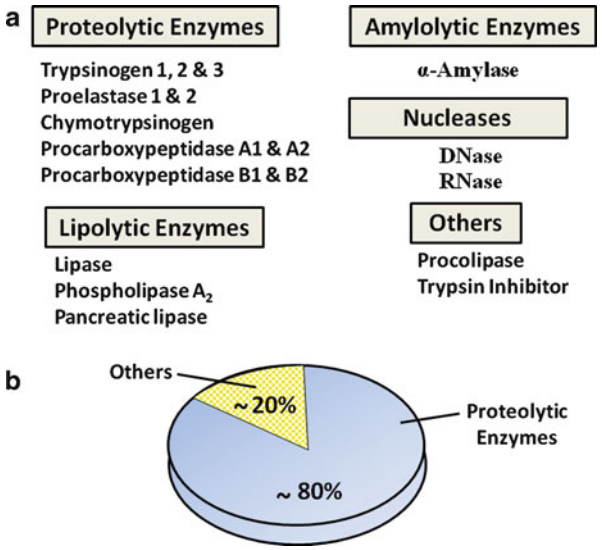

Fig. 4.5 Common proteins of human pancreatic juice. (**a**) These secreted proteins are essential for digestion and absorption of ingested nutrients. (**b**) Proteolytic enzymes make up the majority of proteins that are secreted by pancreatic acinar cells

2.2 Protein Secretion Essential for Digestion

The exocrine pancreas makes and secretes a variety of proteins, most of which are essential for digestion and absorption of ingested nutrients (Fig. 4.5). However, if these proteins were secreted as active enzymes within the parenchyma of the pancreas, the consequences would be potentially disastrous, as extensive tissue destruction would result (**i.e**. ***autodigestion***). To **prevent autodigestion**, the pancreas protects itself in several ways. First, all potentially ***harmful enzymes are made in an inactive or proenzyme form*** and are packaged in zymogen granules within acinar cells. Secreted enzymes remain inactive until their reach the duodenal lumen (Fig. 4.6a). Second, in the duodenum, ***trypsinogen, a major proteolytic enzyme, is converted to active trypsin*** by an enzyme, called ***enterokinase***, a brush-border enzyme expressed by duodenal mucosa. Trypsin catalyzes the activation of more trypsin through hydrolysis of the N-terminal hexapeptide of the trypsinogen molecule, thus rapidly accelerating the entire process. Active trypsin is also essential for activation of several other proteolytic and lipolytic pancreatic enzymes. Thus, the activation site for potentially destructive enzymes is geographically removed from the pancreas and compartmentalized within the duodenal lumen (Fig. 4.6b). Finally, acinar cells make ***trypsin inhibitor***, which is packaged with trypsinogen in zymogen granules. Its role is to activate small amount of trypsin that may form within cells or the body of the pancreas.

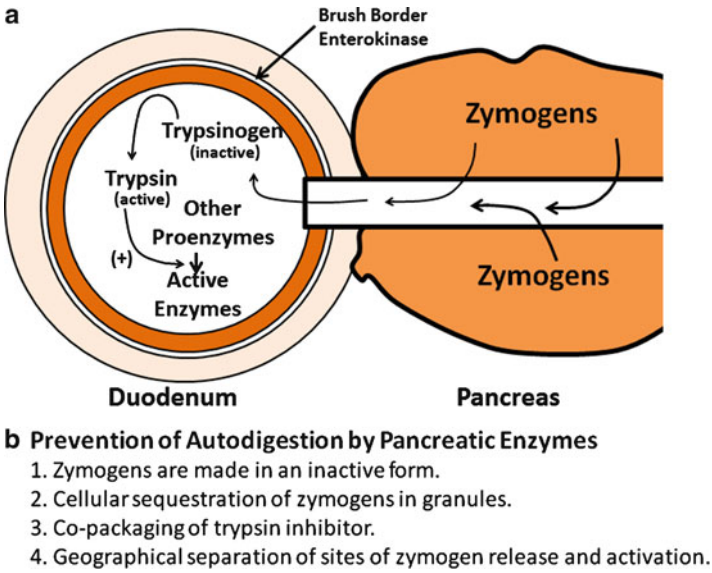

Fig. 4.6 Mechanisms and sites of activation of pancreatic zymogens. (**a**) Secreted enzymes remain inactive until they reach the duodenal lumen. Trypsinogen, a major proteolytic enzyme, is converted to active trypsin by brush-border enterokinase. Trypsin catalyzes the activation of more trypsin, thus accelerating the entire process. Active trypsin is also essential for activation of other proteolytic and lipolytic pancreatic enzymes. (**b**) Mechanisms for preventing autodigestion are shown

Pancreatic juice contains several kinds of hydrolytic enzymes capable of digestive micronutrients (proteins, peptides, fats, carbohydrates, and nucleic acids) into their basic subunits. Proteolytic enzymes make up almost 80 % of all protein found in pancreatic juice (Fig. 4.5b). These include **endopeptidases** (cleaving internal peptide linkages) such as *trypsin* and **exopeptidases** (cleaving from ends of proteins) such as *carboxypeptidases*. Other enzymes include *nucleases*, *amylase* (digestion of carbohydrates), and those involved in lipid digestion such as *lipase, phospholipase* A_2, and *carboxylesterase*. The functional aspects of these enzymes will be discussed in greater depth in the sections on nutritional physiology.

3 Fluid and Electrolyte Transport of the Pancreas

The ***basal volume of pancreatic secretion*** is estimated to be 0.2–0.3 mL/min, although, when stimulated, pancreatic secretion can reach 4.0–4.5 mL/min. The ***daily output of pancreatic juices*** into the duodenal lumen in humans is approximately 2.5 L/day. The fluid secreted by the pancreas represents the combined secretions of both duct and acinar cells, but the compositions of these secretions differ significantly. **Acinar cells** secrete a plasma-like fluid that is predominantly

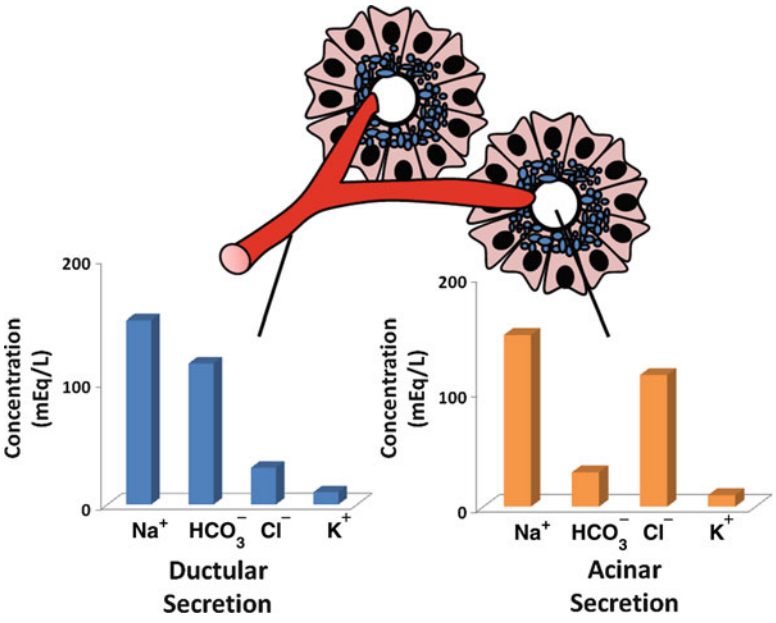

Fig. 4.7 Difference in ionic composition of ductular and acinar fluid. Acinar secretion is a plasma-like fluid that is predominantly sodium chloride. Ductular secretion is predominantly sodium bicarbonate

sodium chloride (Fig. 4.7). The rate of acinar cell fluid secretion is dependent on the rate of enzyme secretion, and the maximal flow rate is much less than that seen in ducts. The primary function of acinar cell fluid secretion therefore is to transport secreted enzymes into the duct system.

Duct cells, on the other hand, secrete a *bicarbonate-rich* fluid, at a considerably variable flow rate of 0–4.0 mL/min depending on the state of pancreatic stimulation. The purpose of the alkaline secretion is to neutralize gastric acid that enters the duodenum, a process essential for achieving optimal conditions for pancreatic enzyme activity. Inadequate bicarbonate secretion with failure to reach a neutral liminal pH, as occurs in ***chronic pancreatitis***, contributes to maldigestion of ingested nutrients seen in this condition.

3.1 Cellular Mechanism for Ductal Bicarbonate Secretion

The cellular mechanisms for bicarbonate secretion by duct cells have been partially elucidated (Fig. 4.8). Briefly, bicarbonate is derived from carbonic acid, which is formed from carbon dioxide and water diffusing in from the interstitial side. Carbon dioxide derived from metabolism is believed to account for less than 5 % of bicarbonate in pancreatic juice. Carbonic anhydrase catalyzes the production of

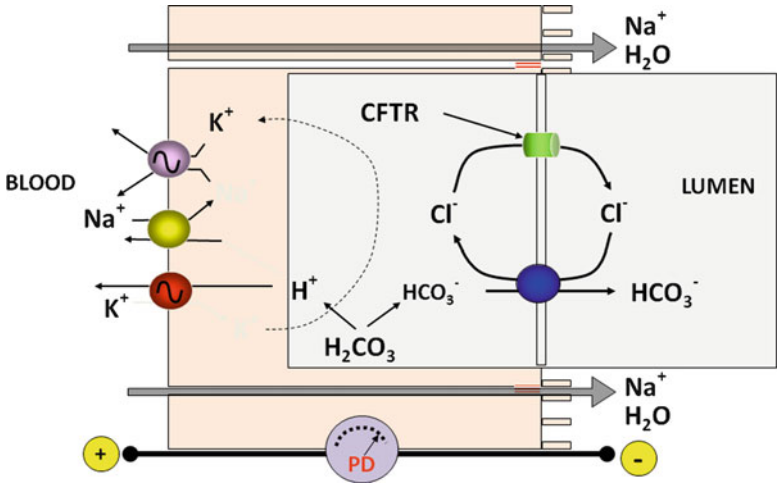

Fig. 4.8 Mechanism of active bicarbonate secretion by pancreatic duct cells. Note that the recycling of Cl^- at the luminal membrane through the cyclic fibrosis transmembrane regulator (CFTR) transporter appears to be important for sustained bicarbonate secretion

HCO_3^- and H^+ from carbonic acid. HCO_3^- is then transported across the luminal plasma membrane by a HCO_3^-/Cl^- exchanger. The major source of luminal Cl^- is now believed to be from the concomitant secretion of the anion via a luminal-membrane Cl^- channel. This channel is regulated by **cAMP-dependent protein kinase** or **cystic fibrosis trans-membrane regulator** (**CFTR**) **protein**, which is defective in cystic fibrosis. The recycling of Cl^- is, therefore, a major factor in determining HCO_3^- secretion. Inhibition of Cl^- channel activity will decrease HCO_3^- secretion. This may explain why ***pancreatic insufficiency*** *develops in some* ***cystic fibrosis*** *patients*, as it results from defective ductular secretions. In such a condition, proteinaceous acinar secretions become concentrated and their precipitation can potentially cause blockage and destruction of pancreatic ducts.

Protons generated during the production of HCO_3^- must be rapidly transported out of the cells or cell pH would drop precipitously. This occurs at the basolateral membrane through **two different mechanisms**. One involves ***Na^+/H^+ exchange***, although it is estimated that the capacity of this pathway is limited especially during maximal HCO_3^- secretion. Therefore, the presence of an ***H^+/K^+-ATPase (proton pump)*** in the basolateral membrane may provide an alternative and perhaps primary mechanism for rapid proton extrusion. This proton pump is different from the one found in parietal cells of the stomach, being functionally more analogous to proton pumps found in the kidney and distal colon. Na^+/K^+-ATPase is also present in the basolateral membrane, necessary for producing favorable electrochemical gradients for Cl^- secretion. Na^+, some K^+, and water accompany HCO_3^- secretion, mostly entering the duct lumen by passive paracellular diffusion, their rate of transport determined by prevailing electrochemical and osmotic forces.

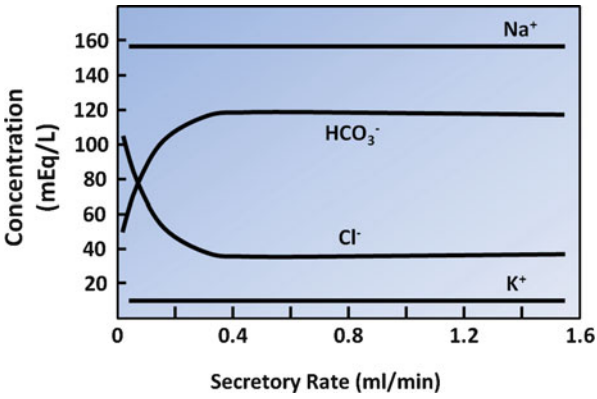

Fig. 4.9 Changes in ionic composition and concentration of pancreatic juice with secretory rate

3.2 Modifications of Electrolyte Composition

Considerable modifications of the pancreatic-juice electrolyte composition occur as secretory rates change. At **low flow rates**, pancreatic fluid is mostly sodium chloride, with small amounts of K^+ and HCO_3^- (Fig. 4.9). However, as **flow rates increase**, the concentration of HCO_3^- increases and a reciprocal decrease in those of Cl^- is observed. It is important to note that Na^+ and K^+ concentrations, the two major cations in pancreatic juice, are not affected by flow rate. Although the mechanisms underlying the rate-dependent alterations in anion composition are not fully understood, several possible explanations have been offered. First, the final concentration of HCO_3^- in pancreatic juices depends on the net HCO_3^-/Cl^- exchange in pancreatic ducts. At low rates, pancreatic juice has greater contact time with ducts, sufficient for ample HCO_3^-/Cl^- exchanger to occur. Pancreatic fluid becomes more Cl^--rich. At faster flow rates, contact time is insufficient for passive HCO_3^-/Cl^- exchanger, and secretions remain HCO_3^- -rich. An alternative mechanism involves the proportions of duct and acinar fluids that are admixed. Acinar fluid is mostly sodium chloride and the maximal flow rate is substantially lower than the maximal flow rate observed in duct cells. At low flow rates, HCO_3^- concentration of pancreatic juice approaches that of duct cell fluid as it becomes the contributor to the total volume.

3.3 Regulation of Electrolyte and Water Secretion

Electrolyte and water secretion by the pancreas is regulated by **neural** and **hormonal** agents. The major **stimulant** for sodium bicarbonate and water secretion is *secretin.* This 27-amino-acid peptide is structurally similar to vasoactive intestinal peptide (VIP), and both hormones are known to stimulate adenylate cyclase in duct cells isolated from the pancreas. The mode whereby cAMP induces

electrolyte secretion probably involves critical phosphorylation events by cAMP-dependent protein kinase (A-kinase). As mentioned above, A-kinase regulation of the apical membrane Cl^- channel (CFTR) may regulate bicarbonate secretion. Several **inhibitors** of fluid and electrolyte secretion by the pancreas have also been identified. These include the *tetradecapeptide somatostatin, pancreatic polypeptide* (released by a meal and apparently under vagal cholinergic control), *glucagon, and possibly peptide YY. Prostaglandins,* particularly those of the E series, have been shown to have inhibitory action on pancreatic bicarbonate fluid secretion in vivo. This is believed to be an indirect effect mediated by the effects of these agents on pancreatic blood flow.

4 Organismal Regulation of Pancreatic Exocrine Secretion

The amount of pancreatic enzymes in the fluid and the timing of their release are critical for the efficient digestion of micronutrients as they enter the duodenum. The pH of gastric chyme must also be quickly neutralized for several reasons. First, acid-pepsin damage to the duodenal mucosa must be prevented. Second, neutral pH is optimal for pancreatic-enzyme activation and function. Finally, neutral pH increases the solubility of bile acids and fatty acids. The mechanisms for maintaining intraluminal pH at or near neutral values are so efficient that only the very proximal duodenum is normally exposed to pH values below 6. To achieve this level of fine control, the timing and extent of pancreatic secretions must be closely integrated with luminal events and digestive demands. The **regulation of pancreatic function** can be divided into **three phases**: ***cephalic***, ***gastric***, and ***intestinal***. These phases are defined on the basis of where the stimulant acts.

4.1 Cephalic-Phase Pancreatic Secretion

The cephalic phase of pancreatic secretion results from **central integration of stimuli** such as *sight* and *smell of food or eating food*. Sham feeding, for instance, can stimulate up to 50 % maximal secretion. These stimuli activate efferent vagal impulses that stimulate the secretion of enzymes and bicarbonate (Fig. 4.10a). This action is partially mediated by cholinergic fibers but may also involve peptidergic neurons.

4.2 Gastric-Phase Pancreatic Secretion

This phase is initiated by the **distention of the stomach by food** and by the **presence of amino acids and peptides** in the lumen (Fig. 4.10b). These stimuli

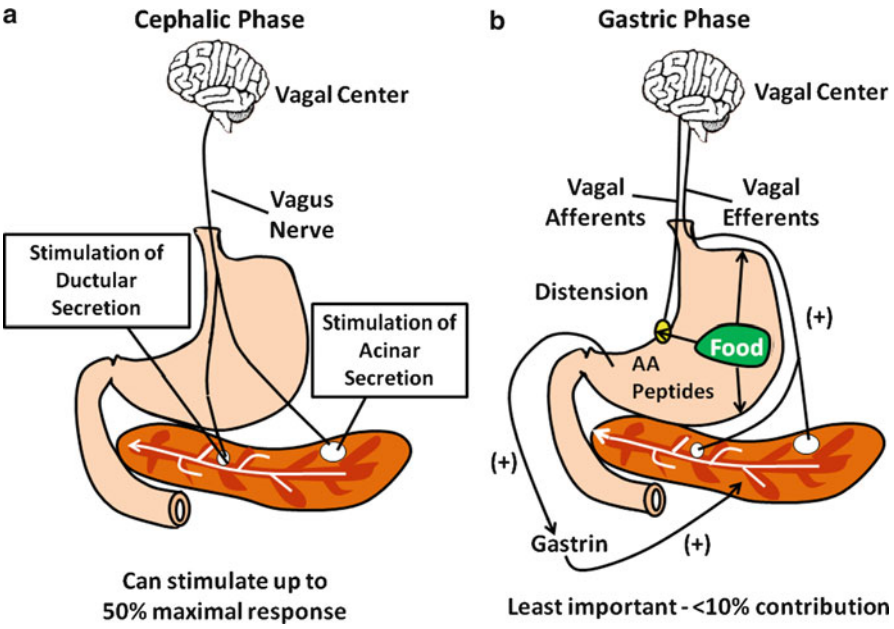

Fig. 4.10 Cephalic and gastric phases of pancreatic exocrine regulation. Meal-stimulated pancreatic secretions are illustrated. (**a**) Cephalic phase and (**b**) gastric phase

activate vagovagal reflexes and gastrin release to stimulate predominantly pancreatic enzyme secretion. ***Vagotomy*** will abolish most of these effects. This phase is probably the *least important*, accounting for less than 10 % of meal-stimulated pancreatic secretions. Pancreatic bicarbonate secretion is also relatively unaffected by stimuli evoked during the gastric phase.

4.3 Intestinal-Phase Pancreatic Secretion

The intestinal phase of pancreatic secretion is physiologically and quantitatively the *most important* (Fig. 4.11). It is initiated by the **entry of gastric chyme** into the intestinal lumen and is primarily mediated by cholinergic reflexes and the release of cholecystokinin (CCK) and secretin. *CCK* and *secretin* are made by **endocrine cells** of the upper small bowel and their release stimulated by both the composition and quantity of food. Luminal fatty acids, for instance, stimulate CCK release, saturated fatty acids being more potent than unsaturated ones. Additionally, relative potency of fatty acids correlates with chain length, i.e. $C_{18} > C_{12} > C_8$. Neutral triglycerides do not stimulate pancreatic secretion unless lipolysis occurs. It is also believed that there are specific receptors for amino acids or oligopeptides on the small intestinal cells capable of eliciting a neural or hormonal response. Stimulation of the

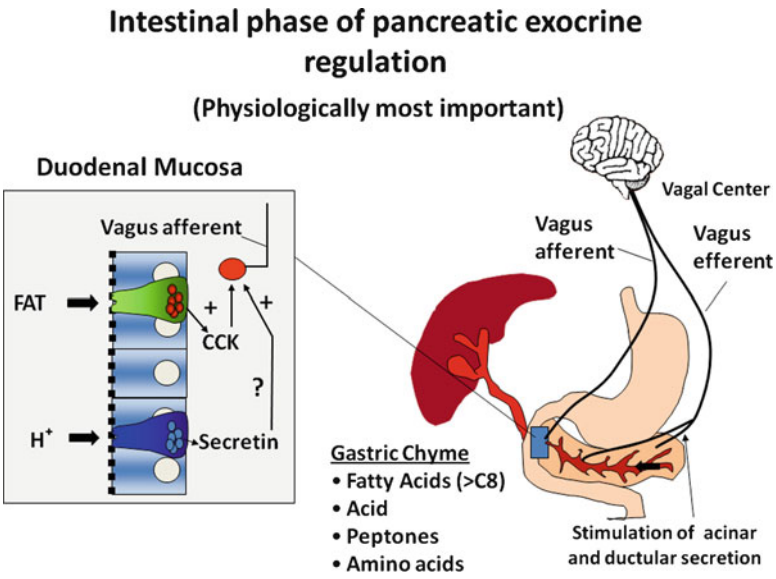

Fig. 4.11 Intestinal phase of pancreatic exocrine regulation. This phase of pancreatic secretion is physiologically and quantitatively the most important. It begins with entry of gastric chyme into the intestinal lumen and is primarily mediated by cholinergic enteric neurons. Ultimate stimulation of acinar secretion is mediated by vagal efferents from the vagal center of the central nervous system

sensory receptors causes the release of peptides such as *CCK, secretin*, and *gastric inhibitory polypeptide (GIP)*, which are crucially involved in activating the second phase of digestion involving coordination of hepatic, biliary, intestinal, gastric, and pancreatic functions.

Regulation of Release of CCK

CCK release from duodenal endocrine cells is stimulated by the presence and composition of luminal contents. Until recently, it was believed that CCK stimulated acinar cell secretion via an *endocrine* action, i.e. entry into the blood circulation and stimulation of distinct CCK receptors expressed by pancreatic acinar cells. However, this notion now appears to be *incorrect*. In fact, the physiological actions of CCK are **predominantly paracrine**, involving afferent cholinergic enteric neurons. Administration of the muscarinic receptor antagonist ***atropine*** or the perivagal or mucosal application of the sensory neurotoxin ***capsaicin*** significantly decreases CCK-stimulated pancreatic acinar cell secretion. These findings place into question on the physiological significance of CCK receptors expressed by pancreatic acinar cells. Although it is possible that these represent a second line of regulation, the issue remains unresolved.

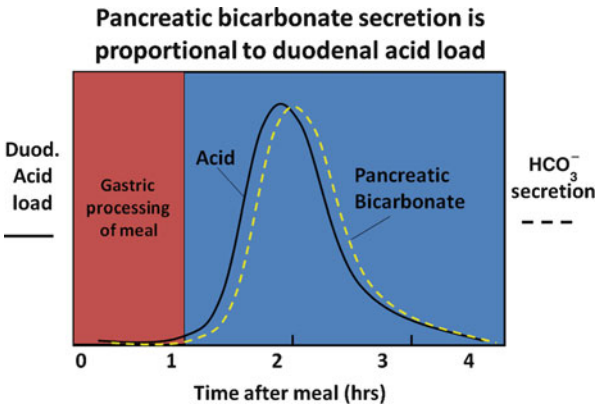

Fig. 4.12 Pancreatic bicarbonate secretion is proportional to the duodenal acid load (Adapted from American Gastroenterological Association Teaching Slide Collection 16 ©, Bethesda, Maryland. Used with permission)

Regulation of Release of Secretin

Increases in secretin stimulated by gastric acid entering the duodenum are tightly controlled and proportional to luminal pH (Fig. 4.12). As a consequence, pancreatic bicarbonate secretion is always proportional to the luminal acid load. At present, the mechanism for this process is believed to involve secretion of secretin by **duodenal endocrine cells** into the blood circulation, although an intermediary role of enteric neurons has not been fully explored. Through an endocrine action, secretin stimulates specific receptors expressed by pancreatic duct cells, initiating bicarbonate secretion. In addition, secretin appears to inhibit gastric acid secretion and motility, allowing time for intestinal digestion before the next bolus of gastric chyme is delivered to the small intestine.

Feedback Mechanism for Pancreatic Secretion

The concept of **feedback regulatory mechanisms** for pancreatic secretions has long been based primarily on studies in rats. Removal of pancreatic proteases from the intestinal lumen or blocking intraluminal proteolytic activity results in stimulation of pancreatic enzyme secretion. The strongest evidence in support of this hypothesis comes from rats in which bile and pancreatic juices are diverted from the intestine. Intestinal perfusion with ***trypsin***, ***chymotrypsin***, or ***elastase*** suppresses CCK release and the pancreatic-enzyme secretory response. Conversely, perfusions with ***amylase*** or ***lipase*** have no effect. Inactivated proteolytic enzymes are ineffective, indicating that the inhibitory action of proteases is due to their proteolytic activity. The precise mechanism by which these proteases inhibit pancreatic secretion is still unknown. Recent studies have suggested that a protease-sensitive protein called **CCK-releasing peptide** is secreted by the proximal small intestine in response to meal-stimulated CCK release from duodenal endocrine cells. During a meal, luminal proteins are the dominant targets of pancreatic protease

activity, making more CCK-releasing factor available for stimulating mucosal endocrine cells. As protein digestion approaches completion, progressively more CCK-releasing peptides become substrates for hydrolysis, reducing the stimulus for more CCK release. During the fasting state, stimulated secretion of the CCK-releasing peptide ceases, and residual peptide in the lumen is rapidly degraded.

Clinical Correlations

Case Study 1

The parents of a small infant bring their child in for evaluation of abnormal bowel movements characterized by loose, bulky, extremely malodorous, and oily stool. The child has failed to gain weight over the past several months and was recently discharged from the hospital for a pulmonary infection. A sweat test is consistent with the diagnosis of cystic fibrosis (CF). Stool examination reveals the presence of fat.

Questions

1. **What GI complication of CF does this child have?**
   Answer: CF is the most common lethal genetic disorder of Caucasians. The genetic basis is now well understood and involves the inheritance of a defective gene called the **cystic fibrosis transmembrane regulator** (**CFTR**). The CFTR gene encodes for a membrane protein that appears to be a cAMP-regulated $C1^-$ channel, although it may have other functions as well. The **clinical manifestations** mainly involve *pulmonary infections* and *complications of the GI tract*. Patients typically have ***abnormal sweat electrolytes,*** characterized by abnormally elevated levels of Na^+ and Cl^-. Although several mutations of CFTR have been described, the most common involved is the **deletion of three nucleotides** encoding a **phenylalanine at position 508**. This causes failure of CFTR to be inserted in the plasma membrane and defective regulation by cAMP-dependent protein kinase.

   CFTR is now recognized to be important in the pathways that mediate pancreatic bicarbonate secretion as discussed in this chapter. The failure of its membrane insertion and activation by cAMP-dependent protein kinase prevents recycling of Cl^- required for vectorial bicarbonate secretion. As a consequence, CF patients have **diminished ductal secretion** that impairs the ability of the pancreas to move pancreatic zymogens to the duodenal lumen. Although the precise pathogenic mechanisms causing pancreatic insufficiency in 85–90 % of CF patients are not known, it is possible that the **ductal inspissation of pancreatic juices** and **activation of zymogens** may lead to *ductal obstruction*, *inappropriate activation of pancreatic enzymes*, and *tissue injury*.
2. **How does pancreatic exocrine insufficiency affect the patient?**
   Answer: CF can be accompanied with ***pancreatic insufficiency*** that causes **maldigestion** (see why below) and **malabsorption** of nutrients (discussed in greater detail in the nutritional physiology chapters). The pancreas has a large functional reserve, as demonstrated by the fact that significant maldigestion in humans with chronic pancreatitis does not occur until the maximal pancreatic secretory capacity for enzyme drops to less than 10 % of normal. In addition to

the **loss of pancreatic enzyme** output (due to tissue destruction), **inadequate bicarbonate secretion** by the pancreas results in failure to adequately neutralize the pH of gastric chyme. Thus, luminal conditions for activation of pancreatic zymogens (best at neutral pH) and micellar formation (necessary for fat digestion and absorption) are suboptimal. This explains this child's ***fatty stools*** and ***failure to gain weight***.

Case Study 2

A 5-year-old boy presents with a history of growth retardation and bulky, oily, malodorous stools. Although he has no history of pulmonary infections, a sweat test for CF is ordered; it is found to be normal. Peroral biopsy of the duodenal mucosa is also normal, and bacterial overgrowth of the bowel is ruled out by a number of diagnostic tests. Because of the extremely high content of stool fat (20 g/day), the possibility of pancreatic insufficiency is entertained. The serum amylase level and imaging studies of the pancreas, however, are normal. Finally, studies to determine the exocrine function of the pancreas are performed. Bicarbonate secretion stimulated by administration of intravenous secretin is found to be normal. However, examination of duodenal contents reveals very low trypsin activity.

Questions

1. **What might be the underlying problem of this patient?**
   Answer: When the pancreatic juice is further analyzed, it appears to have normal protein content, arguing against a problem with pancreatic enzyme production or secretion. However, activities of all pancreatic enzymes are low, suggesting a failure in their activation. This is confirmed, as most ***zymogens*** are still found to be in their ***inactive, proenzyme form***. A mucosal biopsy is performed again and tested for the presence of enterokinase, which is found to be absent. Thus, this child has a **congenital absence of brush-border enterokinase**, which is required for activation of trypsinogen to trypsin (see below). Trypsin in turn activates all other proenzymes of pancreatic juice.
2. **How can you treat this patient?**
   Answers: With **oral replacements of enterokinase**, the child rapidly gains weight and no longer has intestinal symptoms.

Case Study 3

A 58-year-old woman is found to have a slightly elevated 24 hour stool fat content (7 g/day). She is otherwise asymptomatic. She had a history of having a truncal vagotomy 20 years ago for peptic ulcer disease.

Questions

1. **In a patient who has had a vagotomy (surgical interruption of the vagus nerve to the gut), what would be the mechanisms involved in decreased pancreatic secretion thus fat maldigestion and malabsorption?**
   Answer 1: Traditionally, the actions of CCK and possibly secretin on pancreatic function were thought to be mediated by a hormonal pathway. However, recent

studies of humans and animals have dispelled this notion. It is now believed that the **vagal nerve** is essential for mediating CCK-stimulated acinar-cell zymogen secretions (and possibly secretin-stimulated bicarbonate secretion from ducts). CCK is released by endocrine cells of the duodenal mucosa in response to luminal fat and proteolytic products. CCK then stimulates afferent vagal fibers that in turn initiate an effector response emanating from the vagal nuclei of the brainstem. Efferent vagal stimulation thus appears to account for the majority of stimulated acinar cell secretion.

Critical thinking*:*
Small amounts of pancreatic enzymes normally escape from the gland into the plasma, and those that are absorbed across the intestinal epithelia likewise enter the plasma. Because they are of low molecular weight, they appear in the urine. ***Amylase***, for example, will enter the plasma when there is ductal obstruction or rupture or pancreatic destruction. The enzyme is filtered through the glomerular filtration apparatus and along with other proteins is partially reabsorbed by the renal tubules. **A rise in urine amylase** will result from increased liberation of the enzyme from the pancreas or from reduced reabsorption by the renal tubule. Hence the enzyme has been useful in **making the diagnosis of pancreatitis**. Elevated urine amylase is particularly significant in a diagnosis of pancreatitis when the ***renal clearance of amylase*** **far exceeds** the ***renal clearance of creatine*** (a crude measure of glomerular filtration rate).

Further Reading

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