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Pancreas Physiology

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Abstract

In the exocrine pancreas, the relationship between structure and function, as well as between normal and pathological functioning, can be easily understood if presented in a systematic and logical manner. In this chapter, we explain pancreas physiology. We start by explaining the embryological and ontogenetic development of the pancreas and describe the basic anatomical characteristics of the mature gland, i.e. the macro- and microscopic structure, its vascular supply and innervation. These form the foundation necessary to understand the mechanisms of acinar and ductal cell secretion and their regulation, which are covered in the middle part, with an emphasis on the ionic part of the pancreatic juice. In the last part, we focus on the enzymatic part of the pancreatic juice and its role in digestion of all main groups of energy-rich nutrients, i.e. carbohydrates, proteins and lipids. Two main sources of additional information will help the reader grasp the main concepts in pancreas physiology: figures summarize and combine various concepts encountered in the main text, and clinical boxes contain examples of how a given piece of knowledge can be relevant to understand some diseases.

Keywords: pancreas, exocrine, development, embryology, anatomy, vascularization, innervation, physiology, pathophysiology, acinar, ductal, cell, molecular, mechanism, regulation, digestion, secretion, nutrient

1. Introduction

The main aim of this review of pancreas physiology is to facilitate the understanding of other chapters of this book. It is divided into three main sections that deal with the development and the functional anatomy of the pancreas, with the two-compartment model of exocrine pancreas

and the regulation of exocrine secretion and with the role pancreas plays in intestinal digestion of nutrients. Together, these topics shall provide a solid ground to understand etiopathophysiology of the most common pancreatic diseases, their symptoms and crucial clinical characteristics, as well as some key diagnostic and therapeutic principles.

2. Functional anatomy of the pancreas

This chapter is a brief review of human pancreas development and anatomy, with a special emphasis on the exocrine pancreas from both a physiological and a clinical point of view. In other words, this chapter presents developmental and structural basis to understanding pancreas physiology, its blood and lymphatic vasculature, innervation and the integrative regulation of its function, as well as the clinical symptoms and patterns of spreading in cases of malignancy.

2.1. Embryological and ontogenetic development of the pancreas

All parenchymal cell types of the pancreas (acinar, ductal and endocrine cells) are derived from primitive endodermal cells of the foregut [1, 2]. In humans, between the 26th and 28th day of gestation, two endodermal diverticula evaginate from the duodenum, thus forming the dorsal and the ventral pancreatic anlage [3–6]. The dorsal pancreatic bud lies in the dorsal mesentery opposite and above the liver bud. The ventral pancreatic bud develops in the ventral mesentery below the liver bud and connects with the bile duct. During further development, both the ventral bud and the bile duct rotate clockwise, as viewed in the craniocaudal direction, until they reach the dorsal pancreatic bud. Parenchyma of the two buds merges during the 7th week of gestation. The ventral pancreas gives rise to the ventral or lower part of the head of the pancreas that involves also the processus uncinatus, whereas the dorsal pancreas gives rise to the rest of the future pancreas, i.e. the dorsal or upper part of the head, the neck, the body and the tail [7]. Together with parenchyma, the ducts of the primitive pancreas also merge. Ducts of the ventral pancreas and the proximal part of the dorsal pancreas give rise to the main pancreatic duct (of Wirsung). The distal part of the duct of the dorsal pancreas may either obliterate or give rise to the accessory pancreatic duct (of Santorini). In the latter case, the accessory duct drains into the duodenum in the smaller papilla of Santorini that is located orally relative to the larger papilla of Vater [6].

During endoscopic retrograde cholangiopancreatography (ERCP), in approximately 3% of people the so-called anomalous pancreaticobiliary junction (APBJ) can be found. In this variation, the pancreatic duct joins the bile duct a few centimetres proximally from the duodenal wall. Due to a reflux and stasis of a mixture of bile and pancreatic juice in the bile duct and gallbladder, the incidence of gallbladder and bile duct carcinoma is increased in these people [8, 9]. In addition to APBJ, a number of other conditions result from defects in the embryological development of the pancreas, such as the annular pancreas and pancreas divisum, that are reviewed elsewhere [8]. The dual embryological origin of the pancreas also reflects in the smaller size and a tighter arrangement of the lobules in the ventral pancreas

(lower head and the uncinete process), as well as a different cellular make-up of islets of Langerhans and vascular supply (see below) [10].

In newborns, the total weight of pancreas is around 3 g and the volume of the exocrine pancreas increases approximately linearly to 20 years of age [11–13]. During the period of 20–60 years of age, the volume remains stable and then decreases beyond 60 years of age [11] (**Figure 1**).

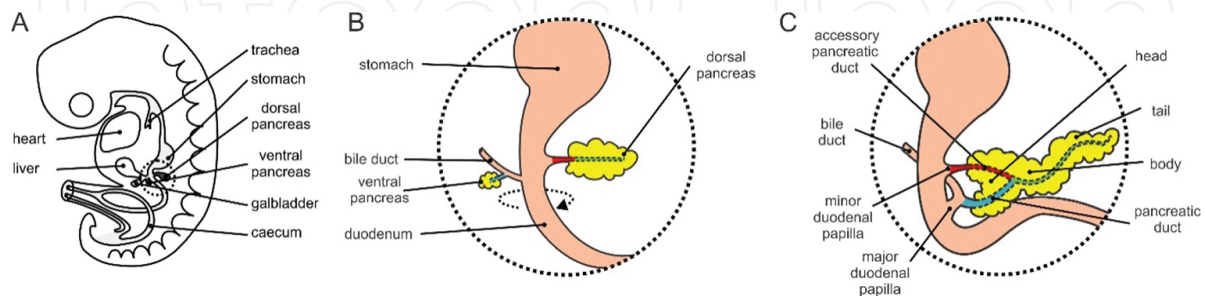


Figure 1. Embryonic development of the pancreas. (A) The position of the pancreatic buds in an embryo at the 5th week of development. (B) During development, the ventral pancreatic diverticulum rotates clockwise to reach its dorsal counterpart. (C) The ventral and dorsal bud as well as their duct merges during development of the gland.

2.2. Macro- and microscopic anatomy of the pancreas

The human pancreas is a large solitary retroperitoneal organ with well-defined outer borders located at the level of the L1 and L2 vertebrae. The gland is 14–18 cm long, 2–9 cm wide and 2–3 cm thick, weighing 50–125 g [11, 14–17]. It is surrounded by a fibrous capsule from which connective tissue septa extend into the gland dividing its parenchyma into distinct lobes and lobules. In contrast to the outer borders, there are no clear-cut macroscopic borders between the major parts in which the pancreas is usually divided for descriptive purposes: the head, the body and the tail. Generally, the left border of the superior mesenteric vein (SMV) is regarded as the border between the C-shaped head aligned with the upper duodenum on the right and the body located underneath the stomach and extending roughly horizontally in the medial plane on the left. The mid-point of the body and tail combined is then arbitrarily defined as the border between the body and the tail, with the tail usually ranging 1.5–3.5 cm in length [14, 17, 18]. Some authors define a fourth and a fifth part, the inferomedial uncinete process that lies beneath the SMV and the superior mesenteric artery (SMA), and the isthmus or neck, which is an approximately 2 cm wide part of the pancreas situated anterior to the SMA and the point where the SMV and the splenic vein (SV) join to form the portal vein [14–17].

Together with the mesenchyma, the exocrine part of the parenchyma amounts to 96–99% of the total pancreas volume (TPV) [14–16]. Each lobe contains several smaller lobes called lobules. In humans, the lobules are 1–10 mm in diameter [19]. The borders between adjacent lobules are incomplete and thus the whole parenchyma is a continuous unit [20]. Each morphologically recognizable lobule is also a single-functional glandular unit draining into a single duct. In turn, each lobule is supplied by 2–9 arterioles, thus each glandular lobule comprises a few so-called vascular or primary lobules, each of which, by definition, receives

a single artery [20]. The remaining 1–4% of TPV contributes the endocrine parenchyma in the form of approximately a million islets of Langerhans, each of which measures around 100 μm and contains approximately a thousand endocrine cells of at least five different types [14].

From a pathophysiological point of view, as a basic microcirculatory unit the primary lobules resemble the liver units of Rappaport, in that different types of ischemic injuries involve different parts of primary lobules. In more proximal obstruction of a pancreatic artery (due to vasoconstriction in shock, for instance), the most peripheral parts of the primary lobule undergo necrosis, whereas in more distal obstruction (due to blockage of a terminal arteriole in malignant hypertension for instance) the most central parts of a lobule undergo necrosis [19, 21].

Finally, each lobule is composed of acini that are dome-shaped clusters of pyramid-shaped acinar cells. Exocrine secretions from apical poles of acinar cells flow into the lumen of the so-called intercalate duct. Intercalated ducts drain into intra-lobular ducts, these in turn into larger inter-lobular ducts and these finally converge into the main pancreatic duct. The main pancreatic duct empties into the duodenum together with the common bile duct. The end parts of both ducts constitute the so-called hepatopancreatic ampulla (of Vater). The ampulla communicates with the duodenal lumen via the major duodenal papilla (of Vater). The pancreas may have one accessory duct (of Santorini) that leads into the duodenum independently from the main duct and about 2 cm ventroproximally to it [8, 20, 22, 23]. Smooth muscle fibres in the wall of the distal part of the common bile duct, the main pancreatic duct and the papilla form a sphincter (of Oddi) [24], whether or not the smooth muscle fibres in the wall of the distal accessory duct form a functional sphincter remains a matter of debate [23].

Impaction of a gall stone in the ampulla is a specific cause of pancreatitis. Somewhat complementary to the situation in APBJ, Opie proposed that the impaction creates a common channel between the pancreatic and the common bile duct and that the entry of bile into the pancreatic excretory system triggers the inflammation in pancreatitis [25].

2.3. Vascular supply of the pancreas

The regional blood flow to the pancreas approximates 1% of the cardiac output, 90% of which is directed to the exocrine part [26]. The arterial supply is derived from the celiac artery and the SMA [15, 27–30]. The neck, body and the tail of the pancreas (i.e. the major part of the dorsal pancreas) are irrigated by pancreatic branches of the splenic artery (SA) and by the dorsal pancreatic artery (DPA) that branches off near the origin of celiac, hepatic or splenic artery. DPA separates into two main branches: the right branch anastomoses with the anterior superior pancreaticoduodenal artery (PDA, see below) and the left branch gives rise to the transverse pancreatic artery (TPA, also termed the inferior pancreatic artery). TPA runs at the inferior border of the body and tail, usually anastomosing with the pancreatica magna artery, which is the largest pancreatic branch of the splenic artery [30, 31]. The head and the uncinate process are supplied by an anterior and a posterior arcade [32–35]. The anterior arcade is

formed by the anterior superior PDA, and the posterior arcade is formed by the posterior superior PDA [33]. The anterior and posterior superior PDA anastomoses with the anterior and posterior inferior PDA, respectively, both stem from the SMA [34, 35]. The uncinate process and the lower head of the pancreas (i.e. the ventral pancreas) are thus supplied by the SMA.

The venous drainage is anatomically less constant and roughly follows the arterial pattern. The splenic vein collects blood from the neck, the body and the tail via multiple small branches [17, 29]. The blood from the head of the pancreas is drained via two arcades. The anterior venous arcade is formed by the anterior superior and inferior pancreaticoduodenal veins (PDV) draining into the superior mesenteric vein. The posterior arcade consists of the posterior superior and inferior PDV. The posterior inferior PDV drains blood into the superior mesenteric vein, whereas the posterior superior PDV drains directly into the portal vein [15, 28, 29]. A number of anastomoses connect the veins and are typically more irregular than arterial anastomoses [15].

The smallest intra-lobular vessels are collectively termed the microvasculature of the pancreas [36]. A physiologically important relationship exists between the endocrine and exocrine tissue at the level of the microvasculature. In the human pancreas, the majority of islets of Langerhans are situated within exocrine lobules and the islet capillaries lead blood to a second capillary network surrounding acini. This arrangement of the two capillary networks in series is named the insulo-acinar portal system and forms an important basis for endocrine influences upon the exocrine pancreas [37–41]. The venous blood from inter-lobular islets flows directly into the inter-lobular veins and this type of flow is named the insulo-venous system. Noteworthy, from both the insulo-venous and -acinar system, the venous blood is ultimately passed to the portal vein [27, 42] (**Figure 2**).

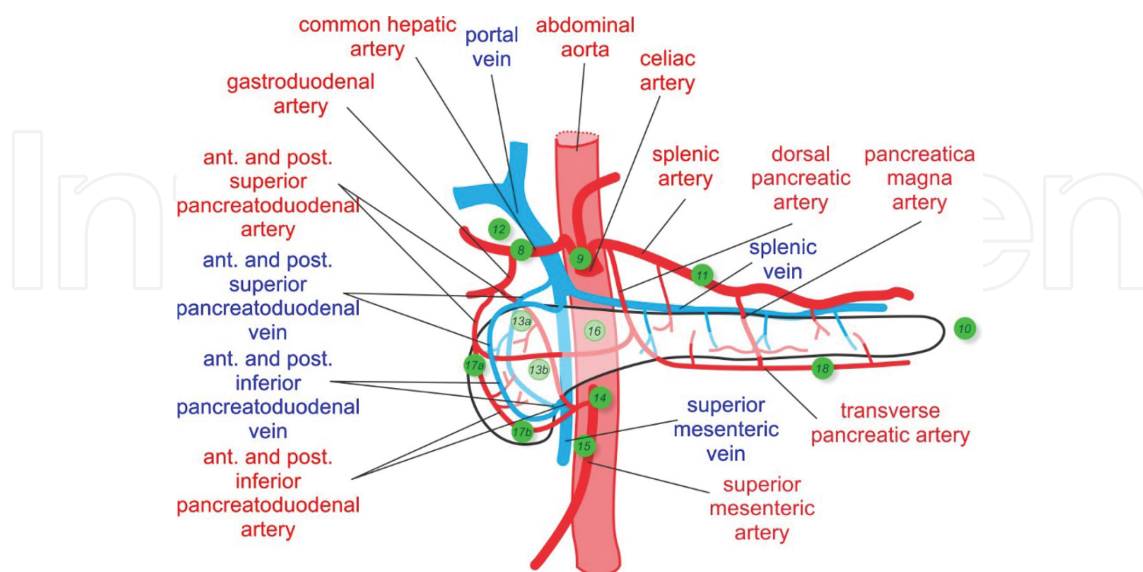


Figure 2. Blood vessels and lymph nodes of the pancreas. The main arteries (red) and veins (blue) supplying pancreas, as well as the main lymph nodes (green), indexed according to the numerical system (see text for details).

The lymphatic system of the pancreas is usually divided into an internal and an external system [43]. The former has been described to some extent only in rodents and is reviewed in detail elsewhere [14, 43]. In brief, the internal lymphatic system arises in the form of blind-beginning intra-lobular vessels distributed in intra-lobular septa, close by smallest blood vessels and ducts, but at a certain distance from acinar cells, with every lobule possessing many such vessels [43, 44]. Intra-lobular vessels drain into inter-lobular vessels running close by inter-lobular blood vessels and ducts in inter-lobular septa. The largest inter-lobular vessels, also called collecting vessels, reach the surface of the gland and drain into the external system [43].

An insufficient removal of extracellular fluid and pancreatic enzymes by the lymphatic overflow system from the interstitium may play an etiological role in pancreatitis. The interstitium and the lymphatic vessels are involved in the inflammatory damage and fibrosis, further hampering the lymphatic drainage and initiating a vicious cycle [43, 44].

The external system consists of large surface lymphatic vessels and regional lymph nodes. Due to the clinical importance of the external system, especially in carcinoma, it has been studied extensively in humans [17, 43, 45–50]. The external lymphatic vessels can be grouped into roughly seven different groups, each of which is associated with a corresponding group of blood vessels. The superior vessels close by the splenic artery and the inferior vessels close by the TPA drain the tail and the left part of the body. The anterosuperior, posterosuperior, anteroinferior and posteroinferior pancreaticoduodenal vessels (close by the arteries of the same name), as well as the gastroduodenal vessels, drain the head of the pancreas and the right part of the body. In general, authors also agree on the anatomical position of the lymph nodes to which the aforementioned vessels drain and on which nodes are most commonly affected in carcinoma of different parts of the pancreas. In contrast, there is much confusion with regard to the nomenclature of the nodes, with a descriptive [17, 46, 51] and a numerical system [49, 52]. In brief, the main groups (with their notation according to the numerical system in parentheses) that collect lymph from the tail and the body are the splenic and gastrosplenic nodes that lie within and superior to the splenic hilum (10), as well as the suprapancreatic (11) and infrapancreatic (18) nodes that lie close by the splenic and inferior pancreatic artery, respectively. The main groups that collect lymph from the head are the hepatic (8) and hepatoduodenal (12), as well as the superior anterior (17a), superior posterior (13a), inferior anterior (17b) and inferior posterior (13b) pancreaticoduodenal nodes. In addition to these nodes that encircle the pancreas, the paraaortic (16), celiac (9), superior mesenteric (14) and the middle colic nodes (15) lie close by the abdominal aorta and its trunks [43, 53]. The nodes tightly surrounding the pancreas and the nodes around the aorta probably do not correspond to first and second barriers of spread, respectively, since they both receive lymph directly from the pancreas as well as from other nodes [43]. Nodes indexed by numbers 1–7 probably do not drain the pancreas [53]. Noteworthy, the centrifugal path from the aforementioned nodes is via cisterna chyli and the thoracic duct [15].

Lymph node involvement is associated with a poor prognosis and is present in approximately four out of five patients with pancreatic cancer [17, 53]. The largely asymptomatic nature of

cancer growth, with jaundice, duodenal obstruction and pain as the most common symptoms appearing late in the course of the disease, probably contributes to the fact that the tumours are detected at an advanced stage. Due to the numerous anastomoses between lymphatic vessels and the fact that obstruction of lymphatic vessels brought about by cancer growth and spread may further alter the already unpredictable routes of drainage, it is extremely difficult to exactly predict the spreading pattern of pancreatic cancer [17, 43, 49]. Tumours originating in the tail and the body most frequently spread to nodes 8, 11, 16 and 18 and only nodes 17 have not been involved in any of the cases [53, 54]. Tumours from the head of the pancreas most frequently spread to nodes 13, 17, 14 and 16, with only nodes 10 and 15 being spared in all cases [49, 50, 53]. It seems that the dual embryological origin of pancreas also influences the spreading pattern of cancer of the head. Tumours from the lower (ventral) head spread to nodes around the SMA (14), in contrast tumours from the upper (dorsal) head spread to nodes around the common hepatic artery (8) and in the hepatoduodenal ligament (12), which is in accordance with the arterial supply (see above) [55].

2.4. Innervation of the pancreas

The pancreas is innervated by sympathetic, parasympathetic and afferent nerve fibres that enter and exit the pancreas together with vessels and follow them also within the pancreatic tissue [36, 56–59]. The somata of preganglionic sympathetic neurons innervating the pancreas reside in the lateral horn of the C8-L3 spinal cord segments and project to paravertebral sympathetic ganglia. Alternatively, some axons do not terminate at synapses within the paravertebral ganglia but continue within splanchnic nerves to synapse within the celiac ganglia and the superior mesenteric ganglion [36, 56, 57]. The tail and the body of the pancreas are supplied by nerve fibres that originate in the celiac plexus and follow the splenic artery and TPA [60]. The majority of nerve fibres to the pancreas supply the head [61]. They originate in the anterior and posterior hepatic plexus. The fibres that enter the uncinate process originate in the superior mesenteric ganglion [60].

As already mentioned, lymph node involvement is one of the most important prognostic factors in pancreaticobiliary tract carcinomas. In general, lymph node metastasis is established by lymphatic invasion; however, tumour cells were shown to be able to spread into the hilum of lymph nodes via neural invasion. The knowledge of patterns of neural architecture may improve curative procedures [62]. Moreover, embryological development of the pancreas served as a useful template for patterns of extrapancreatic nerve plexus invasion of pancreatic head carcinoma [63].

The efferent autonomous nerves in the pancreas have release sites that are not in close contact with cells and thus probably influence many targets at a time [58, 64]. In the exocrine pancreas, the sympathetic terminals contact predominantly the intra-pancreatic ganglia, blood vessels and ducts. Stimulation of sympathetic fibres indirectly inhibits the exocrine secretion by inhibiting intra-pancreatic ganglia and by decreasing supply of fluid via vasoconstriction [36].

The somata of the parasympathetic preganglionic neurons reside in the dorsal motor nucleus of vagus and the nucleus ambiguus [36, 56]. The majority of their axons join the vagus and some the splanchnic nerves and reach the neural plexuses around arteries where they intermingle with sympathetic fibres [61]. The preganglionic parasympathetic neurons finally reach intra-pancreatic ganglia together with vessels supplying them [36, 56]. The parasympathetic ganglia that reside within the inter-lobular septa, lobules and also close to islets receive input not only from parasympathetic preganglionic fibres, but also from other pancreatic ganglia, sympathetic fibres (see above), the myenteric plexus, as well as the sensory fibres (see below) [36]. Postganglionic fibres innervate acinar and ductal epithelial cells, ductal smooth muscle cells and vascular plexuses, as well as other ganglia. These fibres mediate parasympathetic stimulation of secretion from acinar and ductal cells, constriction of ducts, as well as an increase in fluid supply by vasodilation [36, 61].

In the pancreas, sympathetic and parasympathetic afferent fibres can also be found. They contain substance P (SP) or calcitonin gene-related product (CGRP) as neurotransmitters. Sympathetic afferents that innervate both the exocrine and the endocrine tissue join the sympathetic splanchnic nerves and transmit noci- and mechano-receptive sensory information to somata within the dorsal root ganglia and further on to preganglionic sympathetic neurons in the lateral horn of the spinal medulla and probably higher centres [36].

Pancreatic sympathetic innervation is altered in chronic pancreatitis and pancreatic cancer and may contribute to the neuropathic pain and visceral neuropathy in these states [65, 66]. Dorsal root ganglion sympathetic afferent neurons send collaterals to efferent ganglia, representing a neuroanatomical substrate for intrapancreatic monosynaptic vegetative reflexes. For example, SP and CGRP released at intra-pancreatic ganglia inhibit exocrine secretion. Intra-pancreatic ganglia are also contacted by vagal afferents [36].

Somata of vagal afferent neurons reside within the nodose ganglia. They innervate the blood vessels, ducts, acini and islets. However, their centripetal pathways are not well known [36].

3. Integrative physiology of the exocrine pancreas

In this chapter we elucidate the mechanisms by which the exocrine pancreas secretes pancreatic ductal fluid and digestive enzymes under physiological conditions, the regulatory mechanisms that govern its function, and describe the response of pancreatic secretion to a meal. Moreover, this chapter offers some insight into the pathophysiological background of pancreatic diseases related to exocrine pancreas secretion.

3.1. Composition of pancreatic fluid

In humans, the secretion of a neutral, isotonic, Na^+ , Cl^- and H^+ -rich fluid, active digestive proteins, as well as zymogens by the pancreatic acinar cells, and of an alkaline, isotonic and HCO_3^- -rich fluid by the pancreatic ductal cell yields between 1 and 2.5 L of pancreatic fluid

per day, which contains around 20 g of digestive enzymes [67–69]. More than 20 different enzymes are secreted by the acinar cells [70], and some of them are precursor enzymes, such as trypsinogen and chymotrypsinogen. The enzymes released from the acinar cells in an active form are lipases, colipases, A-amylases, collagenases, elastases, ribonucleases and phospholipases A [70, 71].

Human pancreatic fluid contains up to 150 mmol/L of HCO_3^- . Its concentration increases with pancreatic fluid flow rate, and reaches its peak at 30–50% of maximal flow [72, 73]. The Cl^- concentration relates inversely with the pancreatic fluid flow rate and maintains an isotonic osmolality with respect to HCO_3^- . The composition of cations remains fairly constant, irrespective of pancreatic fluid flow rate, with 140 mmol/L Na^+ , and 10–15 mmol/L K^+ . The sum of HCO_3^- and Cl^- concentration closely matches the sum of Na^+ and K^+ concentration. Electrolytes, such as Ca^{2+} , Mg^{2+} , Zn^{2+} , PO_4^{3-} and SO_4^{2-} , are also present, but at minimal concentrations [74–76].

3.2. Regulation of acinar cell secretion

Secretion of digestive enzymes from acinar cells is primarily mediated by acetylcholine (ACh) release from vagal nerve endings and by the intestinal hormone, cholecystikinin (CCK). In addition to its primary role in ductal secretion (see below), the hormone secretin also influences acinar cell function, as does the vasoactive intestinal peptide (VIP) [77, 78].

The pancreas is innervated by postganglionic nerves, which receive input from the preganglionic motor neurons that stem from the dorsal motor nucleus of the vagus (DMV) [79]. ACh mediates its effects on acinar cell secretion via M1 and M3 muscarinic receptors [80], with M3 muscarinic receptors playing a predominant role [81]. The pancreas is also innervated by sensory vagal afferents, which project to the solitary nucleus, where information is integrated and relayed to the preganglionic motor neurons of the DMV, and the two together constitute the so-called dorsal vagal complex [79]. M1 and M3 muscarinic receptors are linked to the Gq/11 family of G-proteins and cause hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP_2) by phospholipase C, yielding inositol 1,4,5-trisphosphate (1,4,5- IP_3) and 1,2-diacylglycerol (DAG) [82–84]. DAG goes on to phosphorylate various proteins via protein kinase C activation, while IP_3 mobilizes Ca^{2+} from internal stores to stimulate amylase secretion [82, 85].

Digestive elements of fats and proteins, such as fatty acids with acyl chains longer than 12 carbon atoms, and amino acids, phenylalanine and tryptophan, are prime secretagogues for CCK secretion by the intestinal I cells. Carbohydrates, on the other hand, do not exhibit particular potency. The mechanisms of CCK action on pancreatic acinar cells seem to exhibit species-specificity [86]. It was thought that the main, if not exclusive, influence of CCK on human acinar cells was mediated via interaction with cholinergic nerves by presynaptic modulation of vagal output [80]. It has been recently shown, however, that CCK can activate human pancreatic acinar cell secretion both directly [87] and indirectly through CCK-A receptors on vagal afferents [77, 79]. Mechanisms of CCK-relayed digestive enzyme secretion have not yet been fully clarified [87]. The CCK-B subtype of CCK receptors seems to be the predominant form in the human pancreas, while the presence of the CCK-A subtype has been difficult to demonstrate [88]. Similar to the M1 and M3 muscarinic receptors, CCK-B receptors

are coupled to the Gq/11 family of G-proteins, and follow a similar signalling pathway to elevate intracellular calcium [83].

An alternative pathway of pancreatic acinar fluid and protein secretion is mediated by secretin and vasoactive intestinal peptide (VIP). By stimulating their respective G α G-protein-coupled receptors an increase in cAMP is observed, which in turn increases PKA activity, leading to secretion [78, 89].

3.3. Molecular mechanisms of acinar cell secretion

In response to stimulation with ACh and CCK, acinar cells secrete an isotonic, plasma-like, protein-rich fluid containing Na⁺, Cl⁻ and H⁺, which is later modified by the ductal cells to form the final fluid [69, 70, 74]. Both secretagogues stimulate mechanisms that cause Ca²⁺ oscillations in the cytosol of acinar cells, which is a signalling mechanism for both fluid and enzyme secretions [90–92].

The fluid secretion of acinar cells is a result of ion transport across the basolateral and apical membranes, as well as paracellular transport mechanisms [90–92]. The driving force for acinar cell fluid secretion stems from the Na⁺/K⁺-ATPase located on the basolateral membrane and from the trans-cellular ion gradient it creates. The Na⁺/K⁺/2Cl⁻ co-transporter NKCC1 on the basal side is responsible for approximately 70% of the Cl⁻ uptake for subsequent secretion by the pancreatic gland. The Ca²⁺- and voltage-activated K⁺ maxi-K channel on the basolateral membrane and others set the acinar cell membrane potential close to the K⁺ diffusion potential. The membrane potential, in turn, serves as the electromotive force for Cl⁻ exit at the apical membrane. Along with the above-mentioned basolateral transport proteins, the Na⁺/H⁺ exchanger NHE1 and the AE2 isoform of the Cl⁻/HCO₃⁻ exchanger family also play a role in basolateral Cl⁻ uptake. Both NKCC1 and NHE1 also provide Na⁺ for the Na⁺/K⁺-ATPase and regulate intracellular pH, keeping it at about pH = 7.2 [90, 93]. Luminal secretion of Cl⁻ occurs via a voltage- and Ca²⁺-activated Cl⁻ channel TMEM16A/Ano1. As Cl⁻ flows through the cell into the lumen of the acinus, Na⁺ follows via the paracellular pathway. The subsequent osmotically driven water flow is mediated by aquaporin AQP1 [70, 74, 93].

Digestive enzymes are stored in zymogene granules at the apical membrane of acinar cells and are released by way of exocytosis. Fusion of granules with the apical plasma membrane releases their contents into the acinar lumen and later on into the small intestine [94]. As with fluid and electrolyte secretion from pancreatic acinar cells, Ca²⁺ ions are the key messenger in triggering and controlling a series of events termed stimulus-secretion coupling, i.e. pathways that regulate digestive enzyme secretion from acinar cells. Upon stimulation with secretagogues, a spike in intracellular Ca²⁺, released from intracellular Ca²⁺ stores, causes fusion of zymogen granules with the plasma membrane [94, 95]. Physiological stimulants can evoke various intracellular Ca²⁺ patterns: (i) global Ca²⁺ oscillations, (ii) Ca²⁺ waves that flow across the cell and (iii) local calcium spikes [96]. Local apical Ca²⁺ spikes, which occur with lower levels of stimulation, as well as global Ca²⁺ spikes will increase the permeability of Ca²⁺-dependent Cl⁻ channels, resulting in fluid secretion. It seems, however, that physiological stimulation yields zymogene granule fusion only when a global Ca²⁺ spike is observed [95].

In acute pancreatitis, a condition, which most frequently occurs due to alcohol abuse and biliary disease, the pro-enzymes stored in acinar cells become activated prematurely, causing autodigestion with inflammation and necrosis of the pancreatic tissue. Under normal conditions, intracellular Ca^{2+} is a key secondary messenger in pancreatic acinar cell secretion. Recently, however, a body of evidence suggests Ca^{2+} is a key initiator of pancreatitis. Noxious stimuli, such as alcohol, long-chain fatty acids and bile acids, provoke extensive Ca^{2+} release from intracellular stores, causing a prolonged and global Ca^{2+} elevation. This kind of abnormal calcium signalling in turn activates trypsinogen that causes pancreatic autodigestion [97–99].

3.4. Regulation of ductal cell secretion

Secretory control of pancreatic ductal cells exhibits great complexity as it involves a variety of receptors on both the basolateral and apical membranes. Activation of these receptors can be a stimulatory or an inhibitory factor in HCO_3^- and fluid secretion [67].

The most important secretagogue for HCO_3^- secretion from pancreatic ductal cells is the peptide hormone secretin [78]. The primary stimulus for secretin release from the neuroendocrine S cells in the proximal duodenum is intra-duodenal pH below 2–4.5, which occurs upon entry of acidic chyme from the stomach. Fatty acids and bile salts are also stimuli for secretin release [78, 100–102]. Upon activation of the secretin receptor on the basolateral side, which is coupled to adenylyl cyclase, increase and accumulation of cAMP are observed. cAMP activates PKA, which in turn phosphorylates the CF transmembrane conductance regulator (CFTR) in the apical membrane of ductal cells [101] and the basolateral $\text{Na}^+\text{-HCO}_3^-$ co-transporter NBCe1-B [74]. Possible alternative routes of cAMP/PKA pathway activation are the release of VIP from vagal nerve terminals, with subsequent VIP receptor VPAC1 activation and beta-adrenergic receptor activation [103]. Vagal nerve fibres release VIP together with the main neurotransmitter ACh. Ductal cells express M2 and M3 muscarinic receptors located on the basolateral membrane [104]. Stimulation with ACh and CCK causes an increase in intracellular Ca^{2+} concentration by stimulating G-protein coupled receptors that activate the phospholipase C pathway, which activates the calcium-activating chloride channels and possibly also the apical $\text{Cl}^-/\text{HCO}_3^-$ exchanger, triggering ductal secretion [67, 105]. The effect of cholecystokinin (CCK) in humans is that of a potentiator of secretin effects on ductal HCO_3^- and fluid output. The enhancing effects of secretin most likely occur by stimulation of vagal afferent fibres [68]. This indicates a synergistic relationship between the Ca^{2+} and cAMP pathways [74]. Ductal cells also express several types of purinergic receptors and intra-luminal application of ATP and UTP results in enhanced HCO_3^- secretion [73, 106]. Luminal ATP causes stimulation of HCO_3^- and pancreatic fluid which quantitatively approaches 75% of maximal secretin stimulation. In contrast, on the basolateral side, ATP inhibits both spontaneous and secretin-evoked secretion by as much as 50% [107].

Substance P, 5-HT, AVP, and the afore-mentioned basolateral ATP fall in the category of potential inhibitory factors in pancreatic HCO_3^- secretion. Although molecular mechanisms of inhibition are not yet fully understood, their role is most likely curtailment of luminal hydro-

static pressure, which precludes enzyme leakage into the pancreatic parenchyma and discontinuation of secretion after a meal [67].

3.5. Molecular mechanisms of ductal cell secretion

One of the earlier models of ductal cell HCO_3^- secretion proposed by Ashton, Argent and Green presupposes intracellular generation of HCO_3^- from CO_2 , and hydration by carbonic anhydrase. The dissociated proton is transported by a Na^+/H^+ exchanger, located on the basolateral membrane, and the HCO_3^- ions are transported into the lumen by a $\text{HCO}_3^-/\text{Cl}^-$ exchanger that is driven by the luminal Cl^- availability. The luminal Cl^- gradient is maintained by a cAMP-activated Cl^- channel, regulated by secretin. Since the exit of HCO_3^- in this model is electrogenic, it is accompanied by outflow of K^+ ions through the cAMP activated maxi-K channels. This model, while providing an explanation for much of what is observed in pancreatic duct cell secretion in many species, is however, limited to a maximum luminal HCO_3^- concentration of about 70 mmol/L. Human pancreatic duct cells, on the other hand, create a luminal HCO_3^- concentration as high as 140 mmol/L and above [67, 68, 108, 109].

In attempts to bring the mechanisms that account for such a high HCO_3^- secretion to light, several models have been proposed [110, 111]. As new information about the identity and properties of ion transporters and channels as well as cellular mechanisms of their action were discovered, a revised two-step model as described below has been suggested.

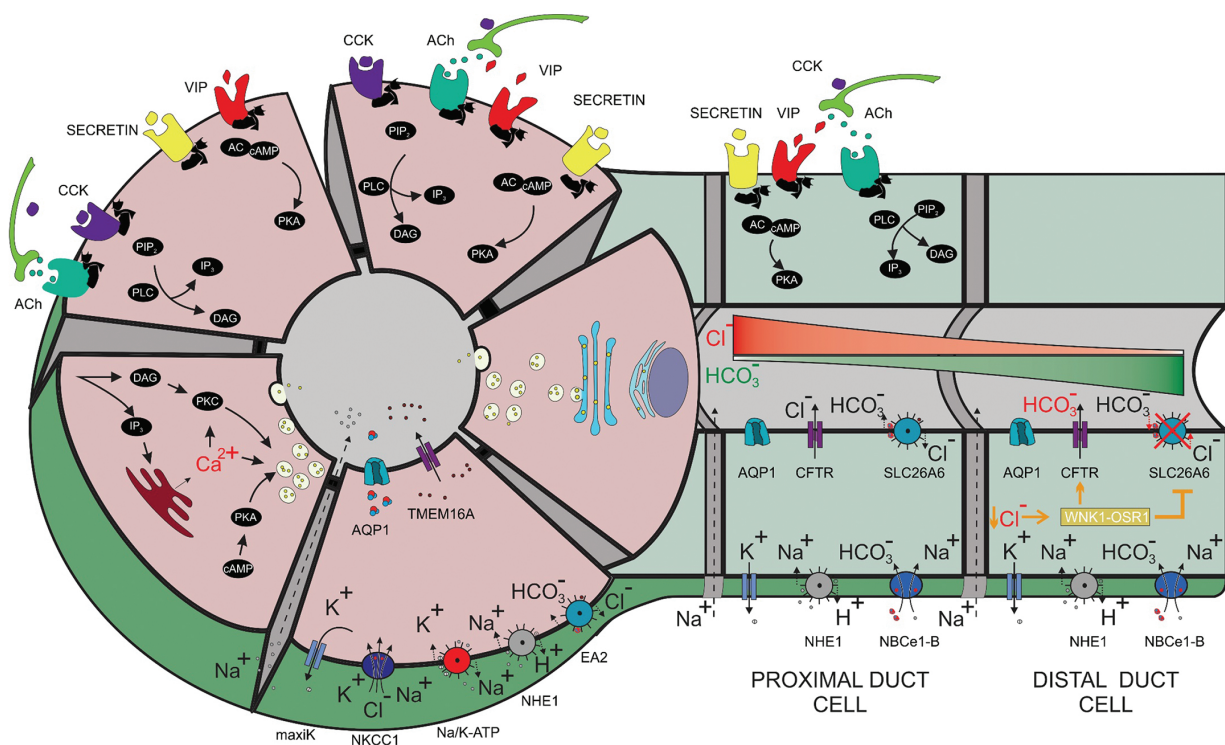


Figure 3. Regulation and molecular mechanisms of secretion in pancreatic acinar and ductal cells. Depiction of molecular mechanisms of pancreatic secretion in the lower half of the image and regulation of pancreatic secretion in the upper half of the image and changes in luminal Cl^- and HCO_3^- concentrations in the lumen (see text for details).

In the proximal duct, HCO_3^- is actively transported and accumulated in the cytosol of ductal cells by a $1\text{Na}^+2\text{HCO}_3^-$ co-transporter NBCe1-B on the basolateral membrane, which is driven by the Na^+ gradient. Secretion of HCO_3^- on the luminal side occurs by way of a $1\text{Cl}^-/2\text{HCO}_3^-$ exchanger SLC26A6, while the CFTR provides a recycling path for Cl^- ions. HCO_3^- secretion drives the translocation of Na^+ ions to the lumen by a paracellular pathway. These two processes create a driving force for water efflux by AQP1 [74]. The proximal duct absorbs a part of the Cl^- and secretes up to 100 mmol/L of HCO_3^- and provides much of the aqueous part of the pancreatic fluid. By the time the fluid reaches the distal segments of the duct, the lumen is Cl^- depleted to approximately 30 mmol/L and due to the active CFTR, the intracellular Cl^- concentration drops to 10 mmol/L or less. Low concentration of Cl^- activates the WNK1-OSR1/SPAK pathway, which results in two events. First, the permeability of CFTR changes in favour of HCO_3^- , making CFTR a route for HCO_3^- secretion. Second, the SLC26A6 is inhibited, which favours HCO_3^- accumulation in the lumen since its active state would most likely result in reabsorption, not secretion as in the proximal lumen [67, 74, 93, 112, 113] (**Figure 3**).

A mutation in the CFTR encoding gene that codes for the chloride and bicarbonate channel involved in pancreatic ductal cell fluid secretion results in a disease called cystic fibrosis, where anomalous fluid secretion results in dysfunction in several organ systems such as the lung, gastrointestinal tract, liver, male reproductive tract and pancreas. Reduced or even absent CFTR function causes a change in ductal fluid composition – decreased pH and fluid volume, and hyper-concentration of fluid components – that is thought to lead to obstruction. As the disease progresses, acinus plugging and dilation provoke epithelial injury and destruction, with inflammation, calcium deposits and fibrosis. These pathological processes lead to indigestion and malnutrition [114, 115].

3.6. Meal-response of pancreatic secretion and the inter-digestive phase

The basal pancreatic exocrine secretion rate reaches approximately 20% of the maximum capacity for enzyme secretion in humans. This basal secretion could be explained by an intrinsic characteristic of the pancreas, stimulation of the gland by low levels of CCK or secretin, or by ACh release [88]. Inhibition of ACh and CCK input reduces pancreatic enzyme secretion by about 50% [116].

The basal pancreatic duct HCO_3^- secretion amounts to only 1–2% in comparison with secretion stimulated with exogenous secretin. Since secretin is the primary regulator of HCO_3^- secretion, basal HCO_3^- mainly parallels plasma secretin levels, along with cholinergic input [88].

In the long term, this is, however, not the full extent of regulation. Inter-digestive pancreatic exocrine function is cyclically coupled with fasting motility phases termed the inter-digestive migratory motor complex (MMC), although they do follow different trends for overall daytime and night time secretory and motor activity [117, 118]. Upon ingestion of a meal, this behaviour is interrupted within minutes. Postprandial enzyme secretion reaches peak levels within the first hour and decreases followed by a stable phase of secretion, only to return to inter-digestive levels in 3–4 h [119].

The meal response of pancreatic secretion can be divided into four phases, i.e. cephalic, gastric, intestinal and inter-digestive phases. The names correspond to the origin of the predominant form of pancreatic secretion control. There is however significant overlap and integration between these regulatory mechanisms in response to a meal. Average pancreatic secretion stimulated by a meal amounts to about 50–60% of the maximum output of the gland [120–122].

The cephalic phase contributes approximately 25% of the meal-response secretion. It is caused by input of visual, olfactory, gustatory and tactile (mastication) sensory modalities. Sham feeding (a process, in which people are allowed to see, smell, taste but not swallow the food) causes pancreatic secretion that is rich in enzymes but low in concentration and volume of HCO_3^- [88]. It amounts to a response that is up to 50% of maximum secretory capacity. The main mediator of the cephalic phase is the vagus nerve with ACh as the dominant neurotransmitter [123].

The gastric phase accounts for about 10% of the meal-response secretion and starts with arrival of food into the stomach. It is regulated by enteropancreatic, vagovagal reflexes, which are stimulated by gastric distension [121].

The majority of the meal-response pancreatic secretion occurs in the intestinal phase. The secretory output amounts to 50–60% of maximal capacity [120]. It starts as the acidic chyme from the stomach, passes into the intestine, where components of the chyme, HCl, bile and bile salts elicit hormonal and neural responses. Hormonal influence on pancreatic secretion in the intestinal phase is mainly the result of CCK and secretin and the amplification of the secretory response by neural influences of the enteropancreatic reflex [121]. Passing of stomach contents into the intestine lowers the luminal pH, which is a signal for the duodenal S cells to release secretin. It, in turn, functions as the main secretagogue for HCO_3^- secretion from the ductal cells and also as an enhancer of enzyme secretion from the acinar cells [77, 102].

4. Role of the exocrine pancreas in digestion

Pancreas plays a crucial role in digestion. Its exocrine part secretes enzymes that are involved in digestion of carbohydrates, proteins and lipids. In this section, we will briefly review the digestive processes in general, and specifically point out the contribution of the pancreatic juice.

4.1. Assimilation of carbohydrates

In the western diet, the mean daily intake of carbohydrates is about 300 g that yield about 1200 kcal in metabolism [124]. Starch, the plant storage polysaccharide, constitutes by far the largest percentage of the carbohydrate intake (70%). About 30% of starch is composed of amylose (a straight polymer of glucose), the remainder of amylopectin (a branched polymer of glucose) [125, 126]. These different constituents of starch require different enzymes for their cleavage. Further 20% of carbohydrates in the food contribute refined sugars (e.g. sucrose, fructose and glucose) and approximately 10% the disaccharide lactose from various sources [127].

Digestion of carbohydrates takes place in two subsequent steps that are separated spatially: (i) digestion in the lumen and (ii) at the enterocyte brush border. Acinar cells of salivary glands (parotid, sublingual and submandibular) and of exocrine pancreas all produce and secrete the closely related enzyme α -amylase [128, 129]. α -amylase is secreted in an active form and has an optimal pH for enzymatic activity at pH=7.0 [130]. It is an endo-enzyme that cleaves internal α -1,4 glycosidic bonds, but not α -1,6 bonds, terminal α -1,4 bonds, or α -1,4 bonds that are next to the branches in the molecular structure [131]. Amylopectin is thus cleaved to maltose and α -limit dextrins, whereas amylose is cleaved to maltose and maltotriose. The reactions seem to yield also a small percentage of free glucose [131].

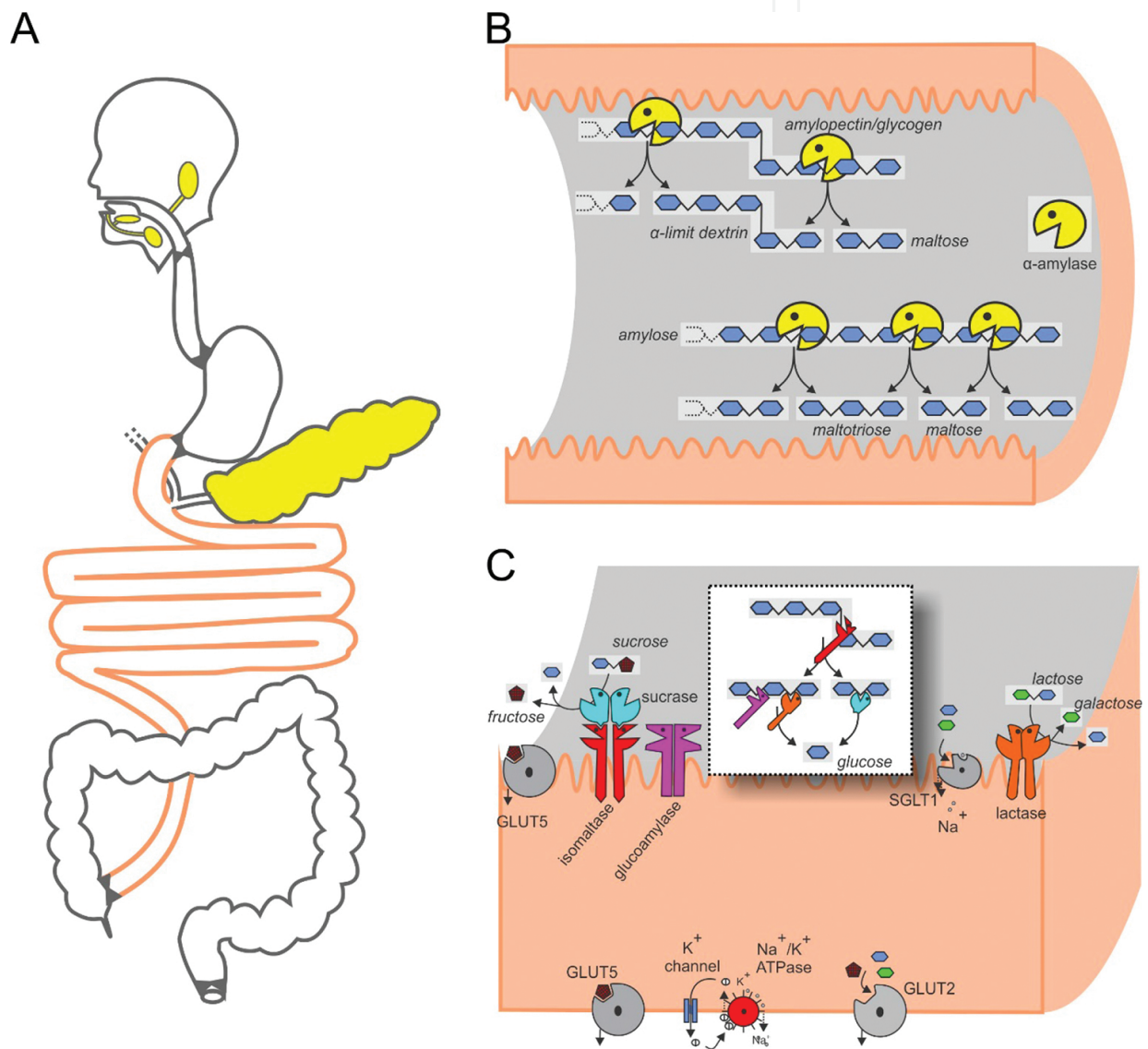


Figure 4. Assimilation of carbohydrates. (A) A schematic representation of the gastrointestinal tract. The origin of digestive enzymes is depicted in yellow and the location of carbohydrate absorption in beige. (B) The luminal phase of digestion critically depends on α -amylase. (C) The brush border phase involves enzymes embedded in the apical membrane of enterocytes. Monosaccharides are then transported across the epithelium by transport proteins in the apical and the basolateral enterocyte membrane.

The digestion of carbohydrates starts with intra-luminal digestion in the oral cavity. This appears not to have an important physiological role, since the salivary α -amylases are mostly inactivated in the acid milieu of the gastric lumen [130]. The activity of salivary α -amylases is partly rescued by occupying the active site of the enzyme with the substrate [132]. The digestion continues in the duodenum with the activity of pancreatic α -amylase, which has a rather neutral pH optimum, brought about by alkalization of acidic chyme from the stomach by duodenal bicarbonate secretion. Contribution of the salivary amylase in starch degradation remains controversial and may become quantitatively more important when mastication time is prolonged [129, 133].

Following the intra-luminal digestion, membrane-bound enzymes of the enterocyte brush border degrade oligosaccharides produced by the luminal digestion to monosaccharides that are then absorbed into enterocytes [134]. The apical membrane of enterocyte brush border contains four major enzymes that act on the luminal side: (i) lactase, (ii) glucoamylase (maltase), (iii) isomaltase and (iv) sucrase [135]. The latter two are located on the same polypeptide chain with two distinctive active sites and are often referred to as the sucrase-isomaltase complex. An essential enzyme for starch digestion is the isomaltase, which is the only enzyme capable of degrading the α -1,6 bond, whereas the other (sucrase, glucoamylase and lactase) are involved in degrading internal α -1,4 bonds. The disaccharides sucrose and lactose are digested by the sucrase and the lactase. The final products of luminal and brush border digestion are the monosaccharides glucose, galactose and fructose, which are then absorbed through the apical membrane via SGLT-1 (glucose and galactose) and GLUT5 (fructose) transporters and through the basolateral membrane via GLUT2 [136–138]. Additionally, GLUT5 transporter in the basolateral membrane may serve as an alternative exit route for fructose (**Figure 4**).

4.2. Assimilation of proteins

Intake of proteins in the western diet amounts to approximately 70–100 g/day, which accounts for 300–400 kcal [124]. In contrast to the carbohydrates, protein digestion starts in the stomach, as virtually no significant proteolytic enzymes are found in saliva. The chief (zymogenic, peptic) cells of the gastric glands synthesize and secrete the pro-enzyme pepsinogen, the inactive precursor of pepsin, which is a proteolytic enzyme specifically suited to act in the acidic gastric milieu [139]. At pH < 5 in the gastric lumen, pepsinogen is spontaneously converted into the active form, pepsin, by cleavage of an N-terminal peptide. At pH values >5.0 and >7.5 pepsin inactivates reversibly and irreversibly, respectively [140]. Pepsin has its pH optimum at pH = 1.5–2.5. Pepsin functions as an endopeptidase, yielding oligopeptides and amino acids [141, 142].

Bulk proteolysis occurs in the small intestine. The pancreatic acinar cells secrete into the duodenum five major proteolytic proenzymes: trypsin, chymotrypsin, elastase and carboxypeptidase A and B [143–145]. First, the proenzyme trypsinogen is activated by the membrane-bound enterokinase to its active form trypsin [146]. The specific expression of enterokinase serves to limit proteolysis to the lumen of the small intestine. Trypsin, in turn, activates additional trypsin molecules and also converts the other four proenzymes, i.e. chymotrypsi-

nogen, proelastase, as well as procarboxypeptidase A and B to their active forms. Carboxypeptidase A and B are ectopeptidases and cleave amino acids at the C-terminus, whereas trypsin, chymotrypsin, and elastase are endopeptidases that cleave polypeptides at specific sites resulting in 2–6 amino acid oligopeptides [144]. The oligopeptides from the lumen are further cleaved by both brush border-bound and intracellular cytosolic peptidases [134].

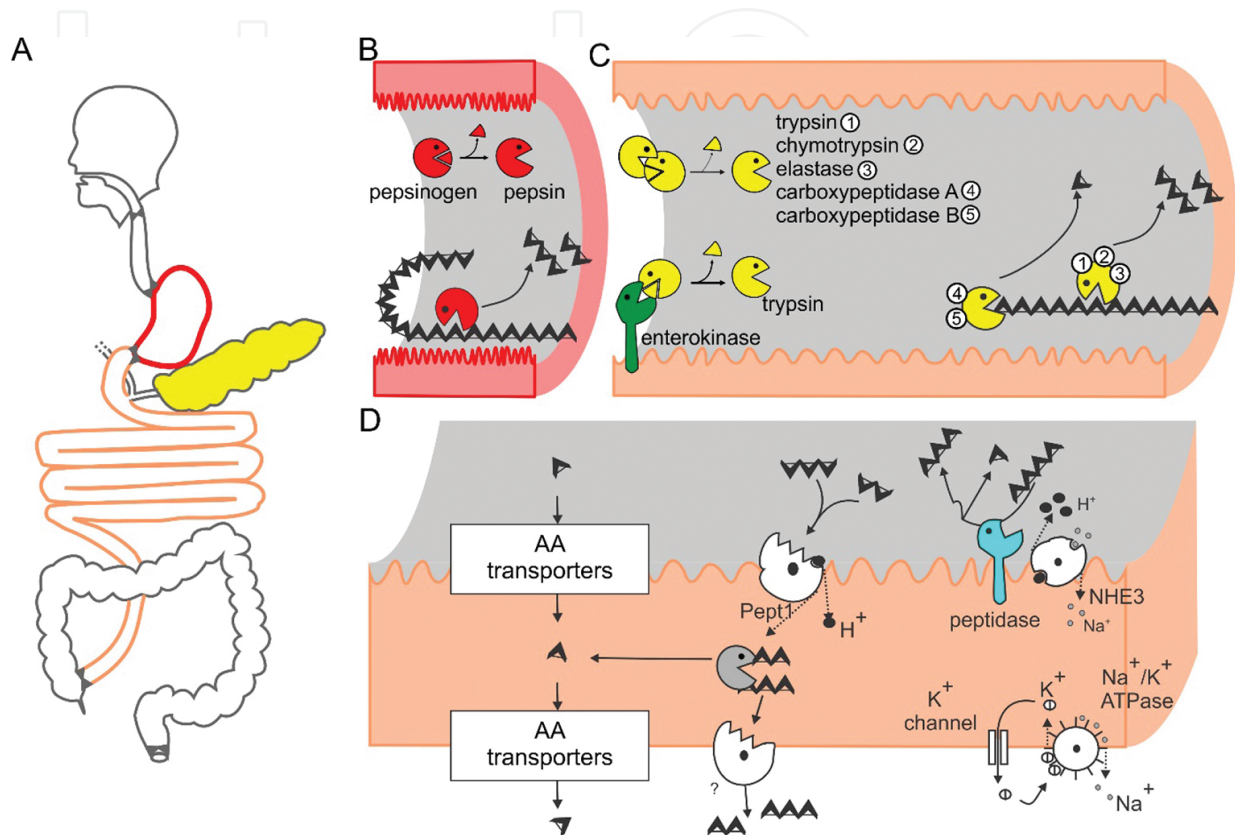


Figure 5. Protein assimilation. (A) A schematic representation of the gastrointestinal tract. Red denotes the start of digestion in the stomach, whereas beige indicates the site of digestion by pancreatic enzymes (indicated in yellow) as well as absorption. (B) Gastric luminal digestion of proteins by pepsin. (C) Intestinal luminal digestion of proteins by trypsin, chymotrypsin, elastase and carboxypeptidase A and B. (D) Brush-border assimilation of proteins involves membrane-bound peptidases, as well as peptone and amino acid (AA) transport mechanisms.

The absorption of oligopeptides and free amino acids differs. The oligopeptides are absorbed through the apical membrane with the PepT1, a H⁺/oligopeptide co-transporter driven by an H⁺ gradient generated by the NHE3 (Na/H exchanger type 3) [147, 148]. The amino acid absorption at the apical and basolateral membrane involves at least seven and five different transport systems, respectively; however, a detailed description of these systems is beyond the scope of this chapter [149, 150] (Figure 5).

4.3. Assimilation of lipids

In the western diet, 60–100 g of lipids are ingested daily, which account for about 500–900 kcal [124]. Most of the ingested lipids are in the form of triacylglycerol (TAG, 90–95%), the rest are in the form of phospholipids (PL, 5%) and cholesterol (C, < 0,5%).

Enzymes for digestion of lipids act in the watery environment of intestinal lumen, and due to their hydrophilic character, they act on the surface of ingested lipids organized in amphiphilic droplets. In the process of emulsification, larger droplets are broken into smaller ones, thereby increasing surface to volume ratio, and, consequently, enzyme efficacy [151]. Emulsification starts with food preparation, and continues in the mouth with mastication and in the gastric and intestinal lumen with churning of the ingested food. Lipid droplets organize such that the core is composed of hydrophobic TAG, whereas amphiphilic PL, C and free fatty acids (FFA) are on the surface [152, 153]. This organization, together with some proteins and carbohydrates stabilizes the products of emulsification.

Digestion of lipids exhibits a large functional redundancy [154]. It starts in the gastric lumen catalysed by the lingual and gastric lipase, together termed pre-duodenal lipase [155, 156]. The former is synthesized by acinar cells of the salivary glands and the latter by gastric chief cells. pH optimum for pre-duodenal lipase is around pH = 4, quite appropriate for the acidic gastric milieu [155, 157]. The enzyme cleaves the first ester bond in the TAG producing diacylglycerol (DAG) and an FFA [158, 159]. It is resistant to cleavage by pepsin but not by pancreatic proteases [156], and therefore functions mostly in the gastric lumen where it digests up to 15% of ingested lipids in a healthy individual. However, they might contribute to some extent to digestion of lipids in the duodenum [151, 157, 160, 161].

Digestion of lipids continues in the intestinal lumen by three major enzymes secreted by pancreatic acinar cells: the (i) pancreatic, (ii) nonspecific (carboxylic ester) lipase and (iii) phospholipase A₂. The pancreatic lipase is active in the presence of a colipase (which is in turn activated by trypsin), in an alkaline pH, in the presence of Ca²⁺ and bile salts [162, 163]. The pancreatic lipase cleaves the first and the third ester bond in TAGs yielding 2-monoacylglycerol (MAG) and FFAs [159, 164]. Phospholipase A₂ acts on the second ester bond in glycerophospholipids, giving rise to lysophospholipid (LPL) and FFAs [162]. It is secreted in an inactive form and requires for its activity an alkaline pH and bile salts. The specificity of the nonspecific lipase is low, notably, and it is able to cleave cholesterol esters and MAG [162]. The quantitative contribution of the nonspecific lipase is relatively low compared with the pancreatic lipase. During infancy, the pancreatic lipase related protein 2 contributes to digestion of lipids [165].

The luminal enzyme activity outlined above, in conjunction with an ever-ongoing emulsification, results in a multi-lamellar envelope developing around the droplet, and consisting of FFAs, bile acids, C, MAG and LPLs [166–168]. The multi-lamellar envelope bursts from the droplets in the form of vesicles that are eventually transformed to mixed micelles (especially under the influence of bile salts) that then finally serve as the main vehicle for absorption of lipids. FFAs enter the enterocyte by (i) collision with the plasmalemma and crossing of the plasmalemma by the flip-flop mechanism, or (ii) by diffusion of non-ionic fatty acids or (iii) by carrier-mediated transport. The latter probably involves the fatty acid binding protein (FABP), the fatty acid transporter protein type 4 (FATP4) and CD36 [169, 170]. MAG, LPLs and C probably enter the enterocyte by means of transport proteins or by simple diffusion. Finally, the FFAs, MAG, LPLs and C are re-esterified within the enterocyte, together with apolipoproteins assembled into chylomicrons, exocytosed into the extracellular space on the basolateral side of the plasma membrane, and reach the systemic circulation via the lymphatic circulation.

In contrast, monosaccharides and amino acids reach the systemic circulation via the portal vein [151, 171] (**Figure 6**).

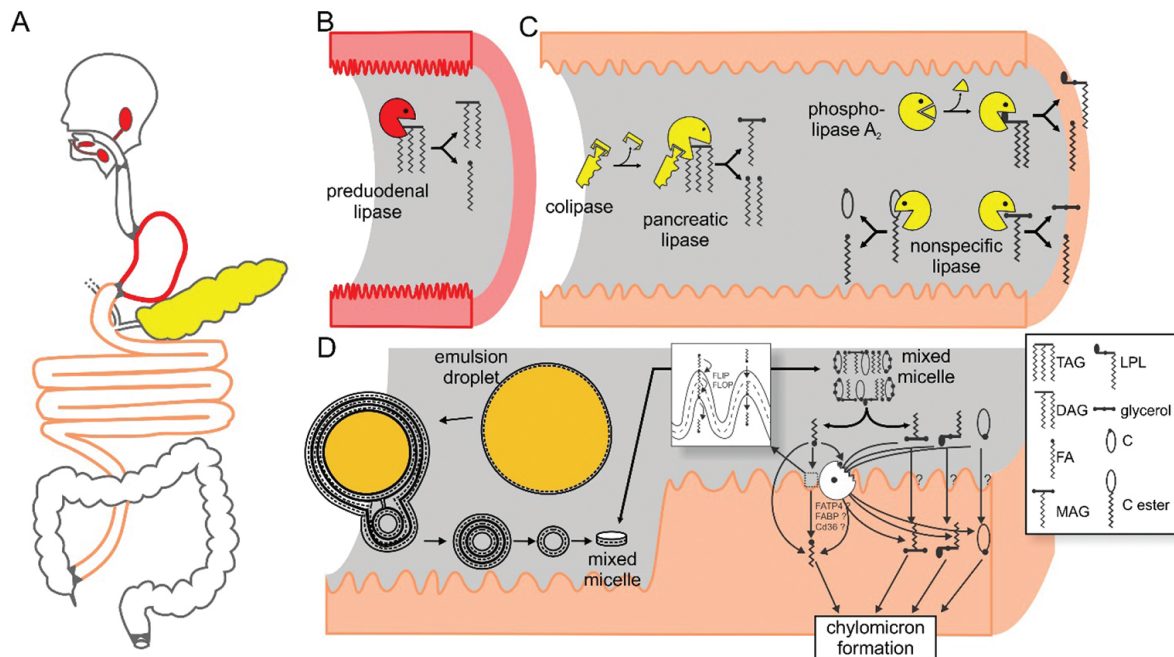


Figure 6. Assimilation of lipids. (A) A schematic representation of the gastrointestinal tract. Digestion starts in the mouth and gastric lumen (red) catalysed by activity of preduodenal lipases. The exocrine pancreas secretes lipolytic enzymes (yellow) that act in the lumen of the small intestine (beige). (B) Gastric luminal digestion of lipids by preduodenal lipase. (C) Intestinal luminal digestion of lipids by pancreatic lipase, phospholipase A₂ and nonspecific lipase. And (D) mixed micelles are formed in the lumen of the small intestine. These act as vehicles for absorption of FFAs, MAG, LPLs and C into enterocytes.

Exocrine pancreatic insufficiency (EPI) due to chronic pancreatitis or cystic fibrosis will eventually result in digestive malfunctioning [172]. However, because of the redundancy of the digestive processes described above, the effect is noticed rather late in the course of the disease [173]. In fact, malabsorption will not present itself until the exocrine pancreas function falls to <10% [174]. Among all the ingested nutrients, assimilation of lipids is most dependent on normal pancreas function. This seems unexpected due to a large redundancy of the lipid digestion, in fact the pre-duodenal lipase output may even increase in the EPI [175] and the pre-duodenal lipases can rescue up to 80% of fat digestion [176, 177]. However, as the destruction of the pancreas progresses, the ductal cells fail to neutralize acidic gastric juice leading to intra-intestinal acidification resulting in bile salt precipitation [175]. Bile salts are necessary for the mixed micelle formation, and this strongly hampers assimilation of lipids. Protein and carbohydrate digestion may have greater digestion potential during EPI due to the fact that the digestion is also initiated independently of pancreas, and continued by the brush-border peptidases and oligosaccharidases that are pancreas-independent. An analogue of the brush-border enzymes is missing in the digestion of lipids; therefore, it is not surprising that in EPI, lipid malabsorption is the most overwhelming problem causing many of the clinical symptoms and signs, leading to weight loss, steatorrhea, abdominal discomfort and a deficit in the lipid-

soluble vitamins (A, D, E, K) [178, 179]. The digestive function can largely be rescued and nutrient malabsorption ameliorated by pancreatic enzyme replacement therapy (PERT), a therapy that involves oral administration of enzyme mixtures consisting of lipases, amylases and proteases [179–181].

5. Conclusions

Despite the ever-growing reductionist record on cell biology of constitutive parts of pancreas (exocrine, ductal and endocrine), whole organ integrative physiology detailing organ development, blood and lymphatic vascularization, innervation and direct links to pancreatic role in intestinal digestion, is rarely part of a single review. The present chapter goes even further and gives examples where this knowledge can provide a basis to understand etiopathophysiology of most common pancreatic diseases, including malignancy. We created a series of images to merge the different cell biological, anatomical and physiological layers to explain modern pancreas function and possible causes for dysfunction.

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References

- [1] Peters J, Jürgensen A, Klöppel G. Ontogeny, differentiation and growth of the endocrine pancreas. *Virchows Arch.* 2000;436(6):527–538. <http://www.ncbi.nlm.nih.gov/pubmed/10917166>.
- [2] Edlund H. Developmental biology of the pancreas. *Diabetes.* 2001;50(Suppl 1):S5–S9. <http://www.ncbi.nlm.nih.gov/pubmed/11272202>.
- [3] Deltour L, Leduque P, Paldi A, Ripoche MA, Dubois P, Jami J. Polyclonal origin of pancreatic islets in aggregation mouse chimaeras. *Development.* 1991;112(4):1115–1121. <http://www.ncbi.nlm.nih.gov/pubmed/1682130>.
- [4] Teitelman G, Alpert S, Polak JM, Martinez A, Hanahan D. Precursor cells of mouse endocrine pancreas coexpress insulin, glucagon and the neuronal proteins tyrosine

hydroxylase and neuropeptide Y, but not pancreatic polypeptide. *Development*. 1993;118(4):1031–1039. <http://www.ncbi.nlm.nih.gov/pubmed/7903631>.

- [5] Habener JF, Kemp DM, Thomas MK. Minireview: transcriptional regulation in pancreatic development. *Endocrinology*. 2005;146(3):1025–1034. doi:10.1210/en.2004-1576.
- [6] Böck P, Abdel-Moneim M, Egerbacher M. Development of pancreas. *Microsc Res Tech*. 1997;37(5–6):374–383. doi:10.1002/(SICI)1097-0029(19970601)37:5/6<374::AID-JEMT2>3.0.CO;2-E.
- [7] In't Veld P, Marichal M. Microscopic anatomy of the human islet of Langerhans. *Adv Exp Med Biol*. 2010;654:1–19. doi:10.1007/978-90-481-3271-3_1.
- [8] Tadokoro H, Takase M, Nobukawa B. Development and congenital anomalies of the pancreas. *Anat Res Int*. 2011;2011:351217. doi:10.1155/2011/351217.
- [9] Tadokoro H, Takase M, Nobukawa B. Unusual fusion between ventral and dorsal primordia causes anomalous pancreaticobiliary junction. *Pathol Int*. 2008;58(8):498–502. doi:10.1111/j.1440-1827.2008.02263.x.
- [10] Fiocca R, Sessa F, Tenti P, et al. Pancreatic polypeptide (PP) cells in the PP-rich lobe of the human pancreas are identified ultrastructurally and immunocytochemically as F cells. *Histochemistry*. 1983;77(4):511–523. <http://www.ncbi.nlm.nih.gov/pubmed/6345484>.
- [11] Saisho Y, Butler AE, Meier JJ, et al. Pancreas volumes in humans from birth to age one hundred taking into account sex, obesity, and presence of type-2 diabetes. *Clin Anat*. 2007;20(8):933–942. doi:10.1002/ca.20543.
- [12] Meier JJ, Butler AE, Saisho Y, et al. Beta-cell replication is the primary mechanism subserving the postnatal expansion of beta-cell mass in humans. *Diabetes*. 2008;57(6):1584–1594. doi:10.2337/db07-1369.
- [13] Rahier J, Wallon J, Henquin JC. Cell populations in the endocrine pancreas of human neonates and infants. *Diabetologia*. 1981;20(5):540–546. <http://www.ncbi.nlm.nih.gov/pubmed/6116638>. Accessed August 4, 2016.
- [14] Dolenšek J, Rupnik MS, Stožer A. Structural similarities and differences between the human and the mouse pancreas. *Islets*. 2015;7(1):e1024405. doi:10.1080/19382014.2015.1024405.
- [15] Bockman DE. Anatomy of the pancreas. In: Go VLW, DiMagno EP, Gardner JD, Lebenthal E, Reber HA, Scheele GA, eds. *The Pancreas: Biology, Pathobiology, and Disease*. 2nd edition. New York: Raven Press; 1993:1–8.
- [16] Rahier J, Goebbels RM, Henquin JC. Cellular composition of the human diabetic pancreas. *Diabetologia*. 1983;24(5):366–371. <http://www.ncbi.nlm.nih.gov/pubmed/6347784>.

- [17] Cesmebasi A, Malefant J, Patel SD, et al. The surgical anatomy of the lymphatic system of the pancreas. *Clin Anat*. 2015;28(4):527–537. doi:10.1002/ca.22461.
- [18] Suda K, Nobukawa B, Takase M, Hayashi T. Pancreatic segmentation on an embryological and anatomical basis. *J Hepatobiliary Pancreat Surg*. 2006;13(2):146–148. doi:10.1007/s00534-005-1039-3.
- [19] Yaginuma N, Takahashi T, Saito K, Kyoguku M. The microvasculature of the human pancreas and its relation to Langerhans islets and lobules. *Pathol Res Pract*. 1986;181(1):77–84. doi:10.1016/S0344-0338(86)80191-1.
- [20] Watanabe T, Yaegashi H, Koizumi M, Toyota T, Takahashi T. The lobular architecture of the normal human pancreas: a computer-assisted three-dimensional reconstruction study. *Pancreas*. 1997;15(1):48–52. <http://www.ncbi.nlm.nih.gov/pubmed/9211492>.
- [21] Takahashi T, Yaginuma N. Ischemic injury of the human pancreas. Its basic patterns correlated with the pancreatic microvasculature. *Pathol Res Pract*. 1985;179(6):645–651. doi:10.1016/S0344-0338(85)80211-9.
- [22] Reichert M, Rustgi AK. Pancreatic ductal cells in development, regeneration, and neoplasia. *J Clin Invest*. 2011;121(12):4572–4578. doi:10.1172/JCI57131.
- [23] Suda K. Histopathology of the minor duodenal papilla. *Dig Surg*. 2010;27(2):137–139. doi:10.1159/000286920.
- [24] Bosch A, Peña LR. The sphincter of oddi. *Dig Dis Sci*. 2007;52(5):1211–1218. doi:10.1007/s10620-006-9171-8.
- [25] Opie EL, Meakins JC. Data concerning the etiology and pathology of hemorrhagic necrosis of the pancreas (acute hemorrhagic pancreatitis). *J Exp Med*. 1909;11(4):561–578. <http://www.ncbi.nlm.nih.gov/pubmed/19867267>.
- [26] Lewis MP, Reber HA, Ashley SW. Pancreatic blood flow and its role in the pathophysiology of pancreatitis. *J Surg Res*. 1998;75(1):81–89. doi:10.1006/jsre.1998.5268.
- [27] Wharton GK. The blood supply of the pancreas, with special reference to that of the islands of Langerhans. *Anat Rec*. 1932;53(1):55–81. doi:10.1002/ar.1090530108.
- [28] Mikami Y, Otsuka A, Unno M. Surgical vascular anatomy and histology. In: *Diseases of the Pancreas*. Berlin, Heidelberg: Springer Berlin Heidelberg; 2008:19–28. doi:10.1007/978-3-540-28656-1_3.
- [29] Meyers MA, Charnsangavej C, Oliphant M. Patterns of spread of disease from the pancreas. In: *Meyers' Dynamic Radiology of the Abdomen*. New York, NY: Springer New York; 2010:259–274. doi:10.1007/978-1-4419-5939-3_10.
- [30] Woodburne RT, Olsen LL. The arteries of the pancreas. *Anat Rec*. 1951;111(2):255–270. <http://www.ncbi.nlm.nih.gov/pubmed/14894836>.
- [31] Bertelli E, Di Gregorio F, Mosca S, Bastianini A. The arterial blood supply of the pancreas: a review. V. The dorsal pancreatic artery. An anatomic review and a radiologic

- study. *Surg Radiol Anat.* 1998;20(6):445–452. <http://www.ncbi.nlm.nih.gov/pubmed/9932331>.
- [32] Bertelli E, Di Gregorio F, Bertelli L, Mosca S. The arterial blood supply of the pancreas: a review. I. The superior pancreaticoduodenal and the anterior superior pancreaticoduodenal arteries. An anatomical and radiological study. *Surg Radiol Anat.* 1995;17(2):97–106, 1–3. <http://www.ncbi.nlm.nih.gov/pubmed/7482159>.
- [33] Bertelli E, Di Gregorio F, Bertelli L, Civeli L, Mosca S. The arterial blood supply of the pancreas: a review. II. The posterior superior pancreaticoduodenal artery. An anatomical and radiological study. *Surg Radiol Anat.* 1996;18(1):1–9. <http://www.ncbi.nlm.nih.gov/pubmed/8685804>.
- [34] Bertelli E, Di Gregorio F, Bertelli L, Civeli L, Mosca S. The arterial blood supply of the pancreas: a review. III. The inferior pancreaticoduodenal artery. An anatomical review and a radiological study. *Surg Radiol Anat.* 1996;18(2):67–74. <http://www.ncbi.nlm.nih.gov/pubmed/8782310>.
- [35] Bertelli E, Di Gregorio F, Bertelli L, Orazioli D, Bastianini A. The arterial blood supply of the pancreas: a review. IV. The anterior inferior and posterior pancreaticoduodenal aa., and minor sources of blood supply for the head of the pancreas. An anatomical review and radiologic study. *Surg Radiol Anat.* 1997;19(4):203–212. <http://www.ncbi.nlm.nih.gov/pubmed/9381324>.
- [36] Love JA, Yi E, Smith TG. Autonomic pathways regulating pancreatic exocrine secretion. *Auton Neurosci.* 2007;133(1):19–34. doi:10.1016/j.autneu.2006.10.001.
- [37] Murakami T, Hitomi S, Ohtsuka A, Taguchi T, Fujita T. Pancreatic insulo-acinar portal systems in humans, rats, and some other mammals: scanning electron microscopy of vascular casts. *Microsc Res Tech.* 1997;37(5–6):478–488. doi:10.1002/(SICI)1097-0029(19970601)37:5/6<478::AID-JEMT10>3.0.CO;2-N.
- [38] Murakami T, Fujita T, Taguchi T, Nonaka Y, Orita K. The blood vascular bed of the human pancreas, with special reference to the insulo-acinar portal system. Scanning electron microscopy of corrosion casts. *Arch Histol Cytol.* 1992;55(4):381–395. <http://www.ncbi.nlm.nih.gov/pubmed/1482603>.
- [39] Merkwitz C, Blaschuk OW, Schulz A, et al. The ductal origin of structural and functional heterogeneity between pancreatic islets. *Prog Histochem Cytochem.* 2013;48(3):103–140. doi:10.1016/j.proghi.2013.09.001.
- [40] Czakó L, Hegyi P, Rakonczay Z, Wittmann T, Otsuki M. Interactions between the endocrine and exocrine pancreas and their clinical relevance. *Pancreatology.* 2009;9(4):351–359. doi:10.1159/000181169.
- [41] Henderson JR, Daniel PM, Fraser PA. The pancreas as a single organ: the influence of the endocrine upon the exocrine part of the gland. *Gut.* 1981;22(2):158–167. <http://www.ncbi.nlm.nih.gov/pubmed/6111521>.

- [42] Brunicardi FC, Stagner J, Bonner-Weir S, et al. Microcirculation of the islets of Langerhans. Long beach veterans administration regional medical education center symposium. *Diabetes*. 1996;45(4):385–392. <http://www.ncbi.nlm.nih.gov/pubmed/8603757>.
- [43] O'Morchoe CC. Lymphatic system of the pancreas. *Microsc Res Tech*. 1977;37(5–6):456–477. doi:10.1002/(SICI)1097-0029(19970601)37:5/6<456::AID-JEMT9>3.0.CO;2-B.
- [44] Regoli M, Bertelli E, Orazioli D, Fonzi L, Bastianini A. Pancreatic lymphatic system in rodents. *Anat Rec*. 2001;263(2):155–160. <http://www.ncbi.nlm.nih.gov/pubmed/11360232>.
- [45] Hoggan G, Hoggan FE. The lymphatics of the pancreas. *J Anat Physiol*. 1881;15(Pt 4):474.1–495. <http://www.ncbi.nlm.nih.gov/pubmed/17231401>.
- [46] Cubilla AL, Fortner J, Fitzgerald PJ. Lymph node involvement in carcinoma of the head of the pancreas area. *Cancer*. 1978;41(3):880–887. <http://www.ncbi.nlm.nih.gov/pubmed/638975>.
- [47] Deki H, Sato T. An anatomic study of the peripancreatic lymphatics. *Surg Radiol Anat*. 1988;10(2):121–135. <http://www.ncbi.nlm.nih.gov/pubmed/3135617>.
- [48] Donatini B, Hidden G. Routes of lymphatic drainage from the pancreas: a suggested segmentation. *Surg Radiol Anat*. 1992;14(1):35–42. <http://www.ncbi.nlm.nih.gov/pubmed/1589845>.
- [49] Kayahara M, Nagakawa T, Kobayashi H, et al. Lymphatic flow in carcinoma of the head of the pancreas. *Cancer*. 1992;70(8):2061–2066. <http://www.ncbi.nlm.nih.gov/pubmed/1327485>.
- [50] Nagakawa T, Kobayashi H, Ueno K, Ohta T, Kayahara M, Miyazaki I. Clinical study of lymphatic flow to the paraaortic lymph nodes in carcinoma of the head of the pancreas. *Cancer*. 1994;73(4):1155–1162. <http://www.ncbi.nlm.nih.gov/pubmed/8313317>.
- [51] Pissas A. Anatomoclinical and anatomosurgical essay on the lymphatic circulation of the pancreas. *Anat Clin*. 1984;6(4):255–280. <http://www.ncbi.nlm.nih.gov/pubmed/6395876>.
- [52] Nagakawa T, Kobayashi H, Ueno K, et al. The pattern of lymph node involvement in carcinoma of the head of the pancreas. A histologic study of the surgical findings in patients undergoing extensive nodal dissections. *Int J Pancreatol*. 1993;13(1):15–22. doi:10.1007/BF02795195.
- [53] Kayahara M, Nagakawa T, Ohta T, et al. Analysis of paraaortic lymph node involvement in pancreatic carcinoma: a significant indication for surgery? *Cancer*. 1999;85(3):583–590. <http://www.ncbi.nlm.nih.gov/pubmed/10091731>.
- [54] Kayahara M, Nagakawa T, Futagami F, Kitagawa H, Ohta T, Miyazaki I. Lymphatic flow and neural plexus invasion associated with carcinoma of the body and tail of the

- pancreas. *Cancer*. 1996;78(12):2485–2491. <http://www.ncbi.nlm.nih.gov/pubmed/8952555>.
- [55] Kitagawa H, Ohta T, Makino I, et al. Carcinomas of the ventral and dorsal pancreas exhibit different patterns of lymphatic spread. *Front Biosci*. 2008;13:2728–2735. <http://www.ncbi.nlm.nih.gov/pubmed/17981748>.
- [56] Ahren B. Autonomic regulation of islet hormone secretion—implications for health and disease. *Diabetologia*. 2000;43(4):393–410. doi:10.1007/s001250051322.
- [57] Gilon P, Henquin JC. Mechanisms and physiological significance of the cholinergic control of pancreatic beta-cell function. *Endocr Rev*. 2001;22(5):565–604. doi:10.1210/edrv.22.5.0440.
- [58] Rodriguez-Diaz R, Caicedo A. Novel approaches to studying the role of innervation in the biology of pancreatic islets. *Endocrinol Metab Clin North Am*. 2013;42(1):39–56. doi:10.1016/j.ecl.2012.11.001.
- [59] Lindsay TH, Halvorson KG, Peters CM, et al. A quantitative analysis of the sensory and sympathetic innervation of the mouse pancreas. *Neuroscience*. 2006;137(4):1417–1426. doi:10.1016/j.neuroscience.2005.10.055.
- [60] Yi S-Q, Miwa K, Ohta T, et al. Innervation of the pancreas from the perspective of perineural invasion of pancreatic cancer. *Pancreas*. 2003;27(3):225–229. <http://www.ncbi.nlm.nih.gov/pubmed/14508126>.
- [61] Tiscornia OM. The neural control of exocrine and endocrine pancreas. *Am J Gastroenterol*. 1977;67(6):541–560. <http://www.ncbi.nlm.nih.gov/pubmed/20775>.
- [62] Kayahara M, Nakagawara H, Kitagawa H, Ohta T. The nature of neural invasion by pancreatic cancer. *Pancreas*. 2007;35(3):218–223. doi:10.1097/mpa.0b013e3180619677.
- [63] Makino I, Kitagawa H, Ohta T, et al. Nerve plexus invasion in pancreatic cancer: spread patterns on histopathologic and embryological analyses. *Pancreas*. 2008;37(4):358–365. <http://www.ncbi.nlm.nih.gov/pubmed/18972625>.
- [64] Ushiki T, Watanabe S. Distribution and ultrastructure of the autonomic nerves in the mouse pancreas. *Microsc Res Tech*. 1997;37(5–6):399–406. doi:10.1002/(SICI)1097-0029(19970601)37:5/6<399::AID-JEMT4>3.0.CO;2-9.
- [65] Ceyhan GO, Demir IE, Rauch U, et al. Pancreatic neuropathy results in “neural remodeling” and altered pancreatic innervation in chronic pancreatitis and pancreatic cancer. *Am J Gastroenterol*. 2009;104(10):2555–2565. doi:10.1038/ajg.2009.380.
- [66] Salvioli B, Bovara M, Barbara G, et al. Neurology and neuropathology of the pancreatic innervation. *JOP*. 2002;3(2):26–33. <http://www.ncbi.nlm.nih.gov/pubmed/11884764>.
- [67] Argent BE, Gray MA, Steward MC, Case RM. Cell physiology of pancreatic ducts. In: Johnson LR, ed. *Physiology of the Gastrointestinal Tract*. 5th edition. New York: Academic Press; 2012:1399–1423. doi:10.1016/B978-0-12-382026-6.00051-8.

- [68] Lee MG, Muallem S. Physiology of duct cell secretion. In: *The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery*. 2nd edition. Oxford: Wiley-Blackwell; 2009:78–90. doi:10.1002/9781444300123.ch7.
- [69] Hegyi P, Maléth J, Venglovecz V, Rakonczay Z. Pancreatic ductal bicarbonate secretion: challenge of the acinar Acid load. *Front Physiol*. 2011;2(July):36. doi:10.3389/fphys.2011.00036.
- [70] Hegyi P, Petersen OH. The exocrine pancreas: the acinar-ductal tango in physiology and pathophysiology. *Rev Physiol Biochem Pharmacol*. 2013;165(April):1–30. doi:10.1007/112_2013_14.
- [71] Petersen OH. Physiology of acinar cell secretion. In: *The Pancreas*. Oxford, UK: Blackwell Publishing Ltd.; 2009:69–77. doi:10.1002/9781444300123.ch6.
- [72] Domschke S, Domschke W, Rösch W, Konturek SJ, Wunsch E, Demling L. Bicarbonate and cyclic AMP content of pure human pancreatic juice in response to graded doses of synthetic secretin. *Gastroenterology*. 1976;70(4):533–536. doi:10.1016/S0016-5085(76)80491-X.
- [73] Ishiguro H, Yamamoto A, Nakakuki M, et al. Physiology and pathophysiology of bicarbonate secretion by pancreatic duct epithelium. *Nagoya J Med Sci*. 2012;74(1–2):1–18. <http://www.ncbi.nlm.nih.gov/pubmed/22515107>.
- [74] Lee MG, Ohana E, Park HW, Yang D, Muallem S. Molecular mechanism of pancreatic and salivary gland fluid and HCO₃ secretion. *Physiol Rev*. 2012;92(1):39–74. doi:10.1152/physrev.00011.2011.
- [75] Denyer ME, Cotton PB. Pure pancreatic juice studies in normal subjects and patients with chronic pancreatitis. *Gut*. 1979;20(2):89–97. <http://www.ncbi.nlm.nih.gov/pubmed/428831>.
- [76] Bro-Rasmussen F, Killmann SA, Thaysen JH. The composition of pancreatic juice as compared to sweat, parotid saliva and tears. *Acta Physiol Scand*. 1956;37(2–3):97–113. doi:10.1111/j.1748-1716.1956.tb01346.x.
- [77] Williams JA. Regulation of pancreatic acinar cell function. *Curr Opin Gastroenterol*. 2006;22(5):498–504. doi:10.1097/01.mog.0000239863.96833.c0.
- [78] Leung PS. The renin-angiotensin system: current research progress in: *The Pancreas*. Vol. 690. Dordrecht: Springer Netherlands; 2010. doi:10.1007/978-90-481-9060-7.
- [79] Chandra R, Liddle RA. Recent advances in pancreatic endocrine and exocrine secretion. *Curr Opin Gastroenterol*. 2011;27(5):439–443. doi:10.1097/MOG.0b013e328349e2e1.
- [80] Singer MV, Niebergall-Roth E. Secretion from acinar cells of the exocrine pancreas: role of enteropancreatic reflexes and cholecystokinin. *Cell Biol Int*. 2009;33(1):1–9. doi:10.1016/j.cellbi.2008.09.008.

- [81] Nakamura K, Hamada K, Terauchi A, et al. Distinct roles of M1 and M3 muscarinic acetylcholine receptors controlling oscillatory and non-oscillatory $[Ca^{2+}]_i$ increase. *Cell Calcium*. 2013;54(2):111–119. doi:10.1016/j.ceca.2013.05.004.
- [82] Noble F, Roques BP. CCK-B receptor: chemistry, molecular biology, biochemistry and pharmacology. *Prog Neurobiol*. 1999;58(4):349–379. doi:10.1016/S0301-0082(98)00090-2.
- [83] Williams JA. Intracellular signaling mechanisms activated by cholecystokinin-regulating synthesis and secretion of digestive enzymes in pancreatic acinar cells. *Annu Rev Physiol*. 2001;63(1):77–97. doi:10.1146/annurev.physiol.63.1.77.
- [84] Shah N, Khurana S, Cheng K, Raufman J-P. Muscarinic receptors and ligands in cancer. *Am J Physiol Cell Physiol*. 2009;296(2):C221–C232. doi:10.1152/ajpcell.00514.2008.
- [85] Mikoshiba K. Role of IP3 receptor signaling in cell functions and diseases. *Adv Biol Regul*. 2015;57:217–227. doi:10.1016/j.jbior.2014.10.001.
- [86] Wang BJ, Cui ZJ. How does cholecystokinin stimulate exocrine pancreatic secretion? From birds, rodents, to humans. *Am J Physiol Regul Integr Comp Physiol*. 2007;292(2):R666–R678. doi:10.1152/ajpregu.00131.2006.
- [87] Murphy JA, Criddle DN, Sherwood M, et al. Direct activation of cytosolic Ca^{2+} signaling and enzyme secretion by cholecystokinin in human pancreatic acinar cells. *Gastroenterology*. 2008;135(2):632–641. doi:10.1053/j.gastro.2008.05.026.
- [88] Liddle RA. Regulation of pancreatic secretion. In: *Physiology of the Gastrointestinal Tract*. Elsevier London; 2012:1425–1460. doi:10.1016/B978-0-12-382026-6.00052-X.
- [89] Chandra R, Liddle R a. Recent advances in the regulation of pancreatic secretion. *Curr Opin Gastroenterol*. 2014;30(5):490–494. doi:10.1097/MOG.0000000000000099.
- [90] Petersen OH. Ca^{2+} signalling and Ca^{2+} -activated ion channels in exocrine acinar cells. *Cell Calcium*. 2005;38(3–4):171–200. doi:10.1016/j.ceca.2005.06.024.
- [91] Cancela JM. Specific Ca^{2+} signaling evoked by cholecystokinin and acetylcholine: the roles of NAADP, cADPR, and IP3. *Annu Rev Physiol*. 2001;63(1):99–117. doi:10.1146/annurev.physiol.63.1.99.
- [92] Yule DI, Lawrie AM, Gallacher DV. Acetylcholine and cholecystokinin induce different patterns of oscillating calcium signals in pancreatic acinar cells. *Cell Calcium*. 1991;12(2–3):145–151. doi:10.1016/0143-4160(91)90016-8.
- [93] Hong JH, Park S, Shcheynikov N, Muallem S. Mechanism and synergism in epithelial fluid and electrolyte secretion. *Pflügers Arch Eur J Physiol*. 2014;466(8):1487–1499. doi:10.1007/s00424-013-1390-1.
- [94] Weiss FU, Halangk W, Lerch MM. New advances in pancreatic cell physiology and pathophysiology. *Best Pract Res Clin Gastroenterol*. 2008;22(1):3–15. doi:10.1016/j.bpg.2007.10.017.

- [95] Low JT, Shukla A, Thorn P. Pancreatic acinar cell: new insights into the control of secretion. *Int J Biochem Cell Biol.* 2010;42(10):1586–1589. doi:10.1016/j.biocel.2010.07.006.
- [96] Thorn P, Lawrie AM, Smith PM, Gallacher DV, Petersen OH. Ca²⁺ oscillations in pancreatic acinar cells: spatiotemporal relationships and functional implications. *Cell Calcium.* 1993;14(10):746–757. <Go to ISI>://A1993MH25500008.
- [97] Gerasimenko JV, Gerasimenko OV, Petersen OH. The role of Ca²⁺ in the pathophysiology of pancreatitis. *J Physiol.* 2014;592(2):269–280. doi:10.1113/jphysiol.2013.261784.
- [98] Lerch MM, Gorelick FS. Models of acute and chronic pancreatitis. *Gastroenterology.* 2013;144(6):1180–1193. doi:10.1053/j.gastro.2012.12.043.
- [99] Li J, Zhou R, Zhang J, Li Z-F. Calcium signaling of pancreatic acinar cells in the pathogenesis of pancreatitis. *World J Gastroenterol.* 2014;20(43):16146–16152. doi:10.3748/wjg.v20.i43.16146.
- [100] Schaffalitzky de Muckadell OB, Fahrenkrug J, Nielsen J, Westphall I, Worning H. Meal-stimulated secretin release in man: effect of acid and bile. *Scand J Gastroenterol.* 1981;16(8):981–988. doi:10.3109/00365528109181015.
- [101] Pallagi P, Hegyi P, Rakonczay Z. The Physiology and pathophysiology of pancreatic ductal secretion: the background for clinicians. *Pancreas.* 2015;44(8):1211–1233. doi:10.1097/MPA.0000000000000421.
- [102] Soleimani M. Impaired pancreatic ductal bicarbonate secretion in cystic fibrosis. *J Pancreas.* 2001;2(4):237–242. doi:v02i04a18 [pii].
- [103] Evans RL, Perrott MN, Lau KR, Case RM. Elevation of intracellular cAMP by noradrenaline and vasoactive intestinal peptide in striated ducts isolated from the rabbit mandibular salivary gland. *Arch Oral Biol.* 1996;41(7):689–694. doi:10.1016/S0003-9969(96)00028-3.
- [104] Szalmay G, Varga G, Kajiyama F, et al. Bicarbonate and fluid secretion evoked by cholecystokinin, bombesin and acetylcholine in isolated guinea-pig pancreatic ducts. *J Physiol.* 2001;535(Pt 3):795–807. doi:10.1111/j.1469-7793.2001.00795.x.
- [105] Jung J, Lee MG. Role of calcium signaling in epithelial bicarbonate secretion. *Cell Calcium.* 2014;55(6):376–384. doi:10.1016/j.ceca.2014.02.002.
- [106] Luo X, Zheng W, Yan M, Lee MG, Muallem S. Multiple functional P2X and P2Y receptors in the luminal and basolateral membranes of pancreatic duct cells. *Am J Physiol.* 1999;277(2 Pt 1):C205–C215. <http://ajpcell.physiology.org/content/277/2/C205.abstract>.
- [107] Ishiguro H, Naruse S, Kitagawa M, Hayakawa T, Case RM, Steward MC. Luminal ATP stimulates fluid and HCO₃⁻ secretion in guinea-pig pancreatic duct. *J Physiol.* 1999;519(Pt 22):551–558. doi:10.1111/j.1469-7793.1999.0551m.x.

- [108] Ashton N, Argent BE, Green R. Characteristics of fluid secretion from isolated rat pancreatic ducts stimulated with secretin and bombesin. *J Physiol*. 1991;435:533–546. <http://www.ncbi.nlm.nih.gov/pubmed/1770448>.
- [109] Whitcomb DC, Ermentrout GB. A mathematical model of the pancreatic duct cell generating high bicarbonate concentrations in pancreatic juice. *Pancreas*. 2004;29(2):e30–e40. doi:10.1097/00006676-200408000-00016.
- [110] Steward MC, Ishiguro H, Case RM. Mechanisms of bicarbonate secretion in the pancreatic duct. *Annu Rev Physiol*. 2005;67(1):377–409. doi:10.1146/annurev.physiol.67.031103.153247.
- [111] Ko SBH, Zeng W, Dorwart MR, et al. Gating of CFTR by the STAS domain of SLC26 transporters. *Nat Cell Biol*. 2004;6(4):343–350. doi:10.1038/ncb1115.
- [112] Steward MC, Ishiguro H. Molecular and cellular regulation of pancreatic duct cell function. *Curr Opin Gastroenterol*. 2009;25(5):447–453. doi:10.1097/MOG.0b013e32832e06ce.
- [113] Park HW, Nam JH, Kim JY, et al. Dynamic regulation of CFTR bicarbonate permeability by $[Cl^-]_i$ and its role in pancreatic bicarbonate secretion. *Gastroenterology*. 2010;139(2):620–631. doi:10.1053/j.gastro.2010.04.004.
- [114] Gibson-Corley KN, Meyerholz DK, Engelhardt JF. Pancreatic pathophysiology in cystic fibrosis. *J Pathol*. 2016;238(2):311–320. doi:10.1002/path.4634.
- [115] Wilschanski M, Novak I. The cystic fibrosis of exocrine pancreas. *Cold Spring Harb Perspect Med*. 2013;3(5):1–17. doi:10.1101/cshperspect.a009746.
- [116] Adler G, Reinshagen M, Koop I, et al. Differential effects of atropine and a cholecystokinin receptor antagonist on pancreatic secretion. *Gastroenterology*. 1989;96(4):1158–1164. <http://www.ncbi.nlm.nih.gov/pubmed/2647576>.
- [117] Keller J, Gröger G, Cherian L, Günther B, Layer P. Circadian coupling between pancreatic secretion and intestinal motility in humans. *Am J Physiol Gastrointest Liver Physiol*. 2001;280(2):G273–G278. <http://ajpgi.physiology.org/content/280/2/G273.short>.
- [118] Vantrappen GR, Peeters TL, Janssens J. The secretory component of the interdigestive migrating motor complex in man. *Scand J Gastroenterol*. 1979;14(6):663–667. doi:10.3109/00365527909181934.
- [119] Keller J, Layer P. Human pancreatic exocrine response to nutrients in health and disease. *Gut*. 2005;54(Suppl 6):vi1–vi28. doi:10.1136/gut.2005.065946.
- [120] Adler G. Regulation of human pancreatic secretion. *Digestion*. 1997;58(Suppl 1):39–41. <http://www.ncbi.nlm.nih.gov/pubmed/9225089>.
- [121] Morisset J. Control of pancreatic secretion in humans. *Adv Med Sci*. 2010;55(1):1–15. doi:10.2478/v10039-010-0013-8.

- [122] Beglinger C, Fried M, Whitehouse I, Jansen JB, Lamers CB, Gyr K. Pancreatic enzyme response to a liquid meal and to hormonal stimulation. Correlation with plasma secretin and cholecystokinin levels. *J Clin Invest*. 1985;75(5):1471–1476. doi:10.1172/JCI111850.
- [123] Anagnostides A, Chadwick VS, Selden AC, Maton PN. Sham feeding and pancreatic secretion. Evidence for direct vagal stimulation of enzyme output. *Gastroenterology*. 1984;87(1):109–114. <http://www.ncbi.nlm.nih.gov/pubmed/6724252>.
- [124] Panel on Macronutrients. *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (Macronutrients)*. Washington, D.C.: National Academies Press; 2005. doi:10.17226/10490.
- [125] Shi Y-C, Capitani T, Trzasko P, Jeffcoat R. Molecular structure of a low-amylopectin starch and other high-amylose maize starches. *J Cereal Sci*. 1998;27(3):289–299. doi:10.1006/jcrs.1997.9998.
- [126] Tester RF, Karkalas J, Qi X. Starch—composition, fine structure and architecture. *J Cereal Sci*. 2004;39(2):151–165. doi:10.1016/j.jcs.2003.12.001.
- [127] Cordain L, Eaton SB, Sebastian A, et al. Origins and evolution of the Western diet: health implications for the 21st century. *Am J Clin Nutr*. 2005;81(2):341–354. <http://www.ncbi.nlm.nih.gov/pubmed/15699220>.
- [128] Horii A, Emi M, Tomita N, et al. Primary structure of human pancreatic alpha-amylase gene: its comparison with human salivary alpha-amylase gene. *Gene*. 1987;60(1):57–64. <http://www.ncbi.nlm.nih.gov/pubmed/2450054>.
- [129] Butterworth PJ, Warren FJ, Ellis PR. Human α -amylase and starch digestion: an interesting marriage. *Starch-Stärke*. 2011;63(7):395–405. doi:10.1002/star.201000150.
- [130] Sky-Peck HH, Thuvasethakul P. Human pancreatic alpha-amylase. II. Effects of pH, substrate and ions on the activity of the enzyme. *Ann Clin Lab Sci*. 1977;7(4):310–317. <http://www.ncbi.nlm.nih.gov/pubmed/20029>.
- [131] Aaberg B, Albaum HG, Arnold A. Aufbau, Speicherung, Mobilisierung und Umbildung der Kohlenhydrate = Formation, storage, mobilization and transformation of carbohydrates. In: *Handbuch Der Pflanzenphysiologie Encyclopedia of Plant Physiology*. 6th edition. Berlin; 1958:1444.
- [132] Rosenblum JL, Irwin CL, Alpers DH. Starch and glucose oligosaccharides protect salivary-type amylase activity at acid pH. *Am J Physiol*. 1988;254(5 Pt 1):G775–G780. <http://www.ncbi.nlm.nih.gov/pubmed/2452576>.
- [133] Lebenthal E. Role of salivary amylase in gastric and intestinal digestion of starch. *Dig Dis Sci*. 1987;32(10):1155–1157. <http://www.ncbi.nlm.nih.gov/pubmed/2443325>.

- [134] Hooton D, Lentle R, Monro J, Wickham M, Simpson R. The secretion and action of brush border enzymes in the mammalian small intestine. *Rev Physiol Biochem Pharmacol*. 2015;168:59–118. doi:10.1007/112_2015_24.
- [135] Van Beers EH, Büller HA, Grand RJ, Einerhand AW, Dekker J. Intestinal brush border glycohydrolases: structure, function, and development. *Crit Rev Biochem Mol Biol*. 1995;30(3):197–262. doi:10.3109/10409239509085143.
- [136] Wright EM, Martín MG, Turk E. Intestinal absorption in health and disease—sugars. *Best Pract Res Clin Gastroenterol*. 2003;17(6):943–956. <http://www.ncbi.nlm.nih.gov/pubmed/14642859>.
- [137] Wright EM, Hirayama BA, Loo DF. Active sugar transport in health and disease. *J Intern Med*. 2007;261(1):32–43. doi:10.1111/j.1365-2796.2006.01746.x.
- [138] Wright EM, Loo DDF, Hirayama BA. Biology of human sodium glucose transporters. *Physiol Rev*. 2011;91(2):733–794. doi:10.1152/physrev.00055.2009.
- [139] Fruton JS. A history of pepsin and related enzymes. *Q Rev Biol*. 2002;77(2):127–147. <http://www.ncbi.nlm.nih.gov/pubmed/12089768>.
- [140] Piper DW, Fenton BH. pH stability and activity curves of pepsin with special reference to their clinical importance. *Gut*. 1965;6(5):506–508. <http://www.ncbi.nlm.nih.gov/pubmed/4158734>.
- [141] Fruton JS. Specificity and mechanism of pepsin action on synthetic substrates. *Adv Exp Med Biol*. 1977;95:131–140. <http://www.ncbi.nlm.nih.gov/pubmed/339686>.
- [142] Powers JC, Harley AD, Myers DV. Subsite specificity of porcine pepsin. *Adv Exp Med Biol*. 1977;95:141–157. <http://www.ncbi.nlm.nih.gov/pubmed/339687>.
- [143] Geokas MC, McKenna RD, Beck IT. Elastase in normal canine pancreas. *Can J Biochem*. 1967;45(6):999–1002. <http://www.ncbi.nlm.nih.gov/pubmed/6034709>.
- [144] Beck IT. The role of pancreatic enzymes in digestion. *Am J Clin Nutr*. 1973;26(3):311–325. <http://www.ncbi.nlm.nih.gov/pubmed/4347665>.
- [145] Neurath H. Proteolytic enzymes past and present: the second golden era. Recollections, special section in honor of Max Perutz. *Protein Sci*. 1994;3(10):1734–1739. doi:10.1002/pro.5560031013.
- [146] Hadorn B. Pancreatic proteinases; their activation and the disturbances of this mechanism in man. *Med Clin North Am*. 1974;58(6):1319–1331. <http://www.ncbi.nlm.nih.gov/pubmed/4610296>.
- [147] Daniel H. Molecular and integrative physiology of intestinal peptide transport. *Annu Rev Physiol*. 2004;66:361–384. doi:10.1146/annurev.physiol.66.032102.144149.

- [148] Daniel H, Kottra G. The proton oligopeptide cotransporter family SLC15 in physiology and pharmacology. *Pflügers Arch Eur J Physiol*. 2004;447(5):610–618. doi:10.1007/s00424-003-1101-4.
- [149] Bröer S. Amino acid transport across mammalian intestinal and renal epithelia. *Physiol Rev*. 2008;88(1):249–286. doi:10.1152/physrev.00018.2006.
- [150] Bröer S. Apical transporters for neutral amino acids: physiology and pathophysiology. *Physiology (Bethesda)*. 2008;23:95–103. doi:10.1152/physiol.00045.2007.
- [151] Mu H, Høy C-E. The digestion of dietary triacylglycerols. *Prog Lipid Res*. 2004;43(2):105–133. <http://www.ncbi.nlm.nih.gov/pubmed/14654090>.
- [152] Linthorst JM, Bennett Clark S, Holt PR. Triglyceride emulsification by amphipaths present in the intestinal lumen during digestion of fat. *J Colloid Interface Sci*. 1977;60(1):1–10. doi:10.1016/0021-9797(77)90250-8.
- [153] Lairon D, Nalbone G, Lafont H, et al. Possible roles of bile lipids and colipase in lipase adsorption. *Biochemistry*. 1978;17(24):5263–5269. <http://www.ncbi.nlm.nih.gov/pubmed/728399>.
- [154] Carrière F, Grandval P, Gregory PC, et al. Does the pancreas really produce much more lipase than required for fat digestion? *JOP*. 2005;6(3):206–215. <http://www.ncbi.nlm.nih.gov/pubmed/15883471>.
- [155] Hamosh M, Scow RO. Lingual lipase and its role in the digestion of dietary lipid. *J Clin Invest*. 1973;52(1):88–95. doi:10.1172/JCI107177.
- [156] Fink CS, Hamosh P, Hamosh M. Fat digestion in the stomach: stability of lingual lipase in the gastric environment. *Pediatr Res*. 1984;18(3):248–254. doi:10.1203/00006450-198403000-00006.
- [157] DeNigris SJ, Hamosh M, Kasbekar DK, Fink CS, Lee TC, Hamosh P. Secretion of human gastric lipase from dispersed gastric glands. *Biochim Biophys Acta*. 1985;836(1):67–72. <http://www.ncbi.nlm.nih.gov/pubmed/4027260>.
- [158] Gargouri Y, Moreau H, Verger R. Gastric lipases: biochemical and physiological studies. *Biochim Biophys Acta*. 1989;1006(3):255–271. <http://www.ncbi.nlm.nih.gov/pubmed/2688745>.
- [159] Cnaan S, Roussel A, Verger R, Cambillau C. Gastric lipase: crystal structure and activity. *Biochim Biophys Acta*. 1999;1441(2–3):197–204. <http://www.ncbi.nlm.nih.gov/pubmed/10570247>.
- [160] Gargouri Y, Pieroni G, Rivière C, et al. Importance of human gastric lipase for intestinal lipolysis: an in vitro study. *Biochim Biophys Acta*. 1986;879(3):419–423. <http://www.ncbi.nlm.nih.gov/pubmed/3778930>.
- [161] Carriere F, Barrowman JA, Verger R, Laugier R. Secretion and contribution to lipolysis of gastric and pancreatic lipases during a test meal in humans. *Gastroenterology*. 1993;105(3):876–888. <http://www.ncbi.nlm.nih.gov/pubmed/8359655>.

- [162] Borgström B. Fat digestion and absorption. In: *Intestinal Absorption*. Boston, MA: Springer US; 1974:555–620. doi:10.1007/978-1-4684-3336-4_1.
- [163] Lowe ME. Structure and function of pancreatic lipase and colipase. *Annu Rev Nutr*. 1997;17:141–158. doi:10.1146/annurev.nutr.17.1.141.
- [164] Mattson FH, Volpenheim RA. The digestion and absorption of triglycerides. *J Biol Chem*. 1964;239:2772–2777. <http://www.ncbi.nlm.nih.gov/pubmed/14216426>.
- [165] Lowe ME. Properties and function of pancreatic lipase related protein 2. *Biochimie*. 2000;82(11):997–1004. <http://www.ncbi.nlm.nih.gov/pubmed/11099796>.
- [166] Patton JS, Carey MC. Watching fat digestion. *Science*. 1979;204(4389):145–148. <http://www.ncbi.nlm.nih.gov/pubmed/432636>.
- [167] Carey MC, Small DM, Bliss CM. Lipid digestion and absorption. *Annu Rev Physiol*. 1983;45:651–677. doi:10.1146/annurev.ph.45.030183.003251.
- [168] Hernell O, Stagers JE, Carey MC. Physical-chemical behavior of dietary and biliary lipids during intestinal digestion and absorption. 2. Phase analysis and aggregation states of luminal lipids during duodenal fat digestion in healthy adult human beings. *Biochemistry*. 1990;29(8):2041–2056. <http://www.ncbi.nlm.nih.gov/pubmed/2328238>.
- [169] Mansbach CM, and Abumrad NA. Enterocyte Fatty Acid Handling Proteins and Chylomicron Formation. In: Johnson LR, ed. *Physiology of the Gastrointestinal Tract*. 5th edition. New York: Academic 30 Press; 2012:1399–1423. doi:10.1016/B978-0-12-382026-6.00051-8.
- [170] Niot I, Poirier H, Tran TTT, Besnard P. Intestinal absorption of long-chain fatty acids: evidence and uncertainties. *Prog Lipid Res*. 2009;48(2):101–115. <http://www.ncbi.nlm.nih.gov/pubmed/19280719>.
- [171] Ratnayake WMN, Galli C. Fat and fatty acid terminology, methods of analysis and fat digestion and metabolism: a background review paper. *Ann Nutr Metab*. 2009;55(1–3): 8–43. doi:10.1159/000228994.
- [172] Berry AJ. Pancreatic enzyme replacement therapy during pancreatic insufficiency. *Nutr Clin Pract*. 2014;29(3):312–321. doi:10.1177/0884533614527773.
- [173] Domínguez-Muñoz JE. Pancreatic exocrine insufficiency: diagnosis and treatment. *J Gastroenterol Hepatol*. 2011;26(Suppl 2):12–16. doi:10.1111/j.1440-1746.2010.06600.x.
- [174] DiMagno EP, Go VL, Summerskill WH. Relations between pancreatic enzyme outputs and malabsorption in severe pancreatic insufficiency. *N Engl J Med*. 1973;288(16):813–815. doi:10.1056/NEJM197304192881603.
- [175] Carrière F, Grandval P, Renou C, et al. Quantitative study of digestive enzyme secretion and gastrointestinal lipolysis in chronic pancreatitis. *Clin Gastroenterol Hepatol*. 2005;3(1):28–38. <http://www.ncbi.nlm.nih.gov/pubmed/15645402>.

- [176] Ross CA. Fat absorption studies in the diagnosis and treatment of pancreatic fibrosis. *Arch Dis Child*. 1955;30(152):316–321. <http://www.ncbi.nlm.nih.gov/pubmed/13249617>.
- [177] Fredrikzon B, Bläckberg L. Lingual lipase: an important lipase in the digestion of dietary lipids in cystic fibrosis? *Pediatr Res*. 1980;14(12):1387–1390. doi:10.1203/00006450-198012000-00026.
- [178] Pezzilli R. Chronic pancreatitis: maldigestion, intestinal ecology and intestinal inflammation. *World J Gastroenterol*. 2009;15(14):1673–1676. <http://www.ncbi.nlm.nih.gov/pubmed/19360910>.
- [179] Fieker A, Philpott J, Armand M. Enzyme replacement therapy for pancreatic insufficiency: present and future. *Clin Exp Gastroenterol*. 2011;4:55–73. doi:10.2147/CEG.S17634.
- [180] Ferrone M, Raimondo M, Scolapio JS. Pancreatic enzyme pharmacotherapy. *Pharmacotherapy*. 2007;27(6):910–920. doi:10.1592/phco.27.6.910.
- [181] Sikkens ECM, Cahen DL, Kuipers EJ, Bruno MJ. Pancreatic enzyme replacement therapy in chronic pancreatitis. *Best Pract Res Clin Gastroenterol*. 2010;24(3):337–347. doi:10.1016/j.bpg.2010.03.006.