12. THE BIOCHEMISTRY OF DIGESTION.

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12.1. Introduction: Functional organization of the digestive system and associated organs

The basic function of the digestive system is the transformation of food into nutrients, so that the body's cells have the necessary molecules for metabolic maintenance and regeneration (Figure 12.1) The gastrointestinal tract (GIT) is a hollow cylinder divided into large functional segments, which vary along its path (10-11 metres). The GIT, that begins in the mouth and ends in the anus, also has several associated glands (salivary glands, liver and pancreas). The main parts of the GIT include:

- Mouth, or oral cavity, is the route of entry or ingestion of food, which is subjected to a mechanical process, mastication, that reduces the food to smaller pieces by the action of chewing (teeth). Food particles are then chemically processed by the enzymes contained in the saliva. In this process, starch is already transformed into maltose.
- Pharynx and esophagus are two consecutive segments that communicate the mouth with the stomach. Pharynx is the place where swallowing occurs; from here on, all digestive processes are involuntary. In the esophagus, the bolus of food passes through the upper sphincter and is propelled by a mechanical process known as peristalsis; then, it crosses the lower sphincter or cardia to reach the stomach.
- Stomach is where food is stored and subjected to the process of digestion. The partially digested food bolus is transformed into the chyme (semi-liquid) after the chemical actions of gastric juices and hydrochloric acid, that in turn destroys the microorganisms that may be present in the food bolus. At the same time, a series of peristaltic waves act on the food in both directions in order to reduce the particle size. Thereafter, the chyme is being gradually eliminated, in a process that depend on the waves, which allow the closure and opening of the pyloric sphincter. Some nutrients such as alcohol, water, and a small part of mineral salts are absorbed in the stomach.

- Small intestine, formed by three segments (duodenum, jejunum and ileum), is where the final stages of digestion occur by means of the chemical action of secretions, such as biliary and pancreatic, and also by mechanical processes, since a large peristalsis is produced in this segment of the GIT. After this treatment digested products are prepared to be absorbed, mainly in the small intestine, that has a large internal surface due to the presence of villi and microvilli. The rest of the chyme passes into the large intestine through the ileocaecal valve.
- Large intestine is the final zone of adjustment of water and ion absorption processes. In addition, it is a storage organ of non-absorbed products that will be eliminated in the form of faeces via the anus, through the anal sphincters (upper and lower).

The main function of sphincters is to prevent reflux, that is, they make sure that the remains of the bolus do not flow back up. In addition, along the tract there are glandular structures, that are invaginations of the tube wall which empty their secretions into the intestinal lumen. This is the case of Brunner glands, that secrete large amounts of HCO_3^- into the duodenum. In general, the main function of the GIT is the administration of water, electrolytes and nutrients to the body, as well as the excretion of food residues and products of liver metabolism.

The average residence times of the food along the different segments of the digestive tract, in theoretical terms, are one minute in the mouth, 2 to 3 seconds in the esophagus, 2 to 4 hours in the stomach, 1 to 4 hours in the small intestine and from 10 hours to several days in the colon. In any case, these residence times are a function of the type of macronutrients that form the food, as long as there is no associated pathology.

12.1.1. Gastrointestinal wall

This is the wall surrounding the lumen of the gastrointestinal tract, that acts as a mechanical, biological, and functional barrier between the lumen content of the intestine and our internal environment. It consists of several types of tissues superimposed on concentric layers (Figure 12.2):

- The mucosa is the inner layer of the GIT, it surrounds the lumen and is in direct contact with digested food (chyme). The mucosa is formed by microvilli, villi, and invaginations or sacs formed in the epithelium, known as crypts. It consists of three parts:
    - The epithelium, the innermost layer, is where most of the processes of digestion, absorption and excretion occur.
    - Lamina propria is a layer of connective tissue within the mucosa.

- Muscularis mucosae is a thin layer of smooth muscle.

Each part of the GIT and associated organs have a highly specialised mucosa .

- The submucosa is a layer of dense disordered connective tissue located underneath the mucosa that contains blood vessels, lymphatic vessels, nerve fibres (plexuses) and prolongations of mucosal glands.
- The muscular layer or muscularis propria is in turn composed of two layers and presents a variable thickness depending on the part of the GIT. The muscle of the inner layer is arranged in circular rings around the tract, while the muscle of the outer layer is arranged longitudinally. The stomach has an extra inner oblique layer. The coordinated contractions of these layers, known as peristalsis, drives food through the gastrointestinal tract. Peristalsis is controlled by the myenteric plexus or Auerbach's plexus, that is located between the longitudinal and circular muscular layers. Peristaltic activity is initiated by the myenteric interstitial cells of Cajal (ICCs), which are responsible for creating the slow wave bioelectric potential leading to smooth muscle contraction. ICCs are mediators of enteric neurotransmission.
- The serosa layer is responsible for covering the intraperitoneal regions of the GIT (those parts suspended by the peritoneum). This structure consists of connective tissue covered by a simple squamous epithelium, called the mesothelium, which reduces frictional forces during digestive movements. The intraperitoneal regions include most of the stomach, first part of the duodenum, all of the small intestine, caecum and appendix, transverse colon, sigmoid colon and rectum. These parts of the tract have mesentery. Retroperitoneal regions include the oral cavity, esophagus, pylorus, distal duodenum, ascending colon, descending colon and anal canal.

Along the GIT there are the organs associated with the alimentary canal, such as the liver with the gallbladder and the pancreas. The liver secretes bile into the duodenum, whereas the pancreas, a gland of mixed origin, secretes pancreatic juice in the duodenum and hormones that control sugar levels into the blood.

12.1.2 Gastrointestinal blood flow: splanchnic circulation

The digestive system and associated organs have their own blood circulation, splanchnic circulation, which passes through the liver, thus allowing the reticuloendothelial cells that line sinusoids to eliminate bacteria and other particles that can penetrate the general circulation. This blood flow allows

the transport of absorbed nutrients to the cells and hence to the entire organism. Water-soluble nutrients (proteins, carbohydrates) are transported to the liver through the portal vein; by contrast, lipid molecules pass to the general circulation via the lymphatic vessels. Hepatic cells (hepatocytes) temporarily take up and store between 1/2 and 2/3 of the absorbed nutrients.

The splanchnic circulation receives 25% of the cardiac output. Blood flow is proportional to gastric activity, thus, in periods between meals activity is minimal, whereas during postprandial periods the activity is maximal.

12.1.3 Neural regulation of gastrointestinal function

The gastrointestinal tract also has its own nervous system, the enteric nervous system ("the brain of the GIT"), that is localised throughout the entire tract, from the esophagus to the anus. This intrinsic innervation is composed of two intramural plexuses, the submucosal (Meissner's) plexus and the myenteric (Auerbach's) plexus, that control the movements and secretions of the GIT (Figure 12.3). The enteric nervous system regulates local function through short reflexes.

The submucosal plexus or Meissner's plexus increases tonic contraction of the intestinal wall, the intensity of rhythmic contractions, and the contraction rate of excitation waves along the intestine. In addition, it regulates the activity of the mucosa, playing an important role in the control of the secretions of the digestive tract and local blood flow. Some neurons of the Meissner's plexus are inhibitory (relaxation in the sphincters). Auerbach's plexus regulates much of the motility of the digestive tract, that is, muscle contractions. Enteric neurons secrete different neurotransmitters (Table 12.1).

The extrinsic innervation is formed by the autonomic system (sympathetic and parasympathetic) that coordinates the function through long reflexes. Sensory nerve endings send afferent fibres to both plexuses and the central nervous system, while receiving efferent information from the autonomic nervous system. On the other hand, sensory nerve endings can trigger local reflexes inside the intestine.

Some sympathetic fibres innervate the smooth muscle (blood vessels) of the digestive tract and cause vasoconstriction while others innervate secretory cells. On the other hand, parasympathetic innervation is provided by the vagus nerve and goes from the esophagus to the transverse colon. The rest of the colon, rectum and anus receive innervation through the pelvic nerves.

The activation of the sympathetic nerves inhibits the secretory motor activities of the digestive system and causes the contraction of the smooth musculature in the sphincters. The activation of parasympathetic nerves stimulates gastrointestinal motor and secretory activity

12.1.4 Chemical regulation of gastrointestinal function

The gastrointestinal tract is regulated by a series of hormones that are synthesised and secreted in the digestive system and act in an autocrine, paracrine and/or endocrine manner, regulating both its motor activity and its secretory activity (Chapter 14). Autocrine means that cells respond to molecules secreted by themselves; paracrine manner occurs when a sensor cell releases a chemical messenger or regulatory peptide that acts on nearby target cells, by diffusion through the interstitial space; endocrine describes the process in which a sensing cell responds to the stimulus by secreting a peptide or regulatory hormone that travels through the bloodstream to target cells away from the secretion point.

12.1.5 Membrane potential in the GIT

As a result of the selective permeability of biomembranes and the action of multiple membrane transporters, there is an uneven distribution of charges across the cell membranes, in such a way that there are more negative charges inside the cell than outside. This results in an electric potential difference known as membrane potential (Chapter 7, Figure 7.2). There are two basic patterns of electrical activity across the membranes of smooth muscle cells, slow waves and spike potentials (Figure 12.4):

- Slow waves are fluctuations in the resting membrane potential (see below), whose intensity vary between 5 and 15 millivolts (mV), and show a frequency of 3 waves per minute in the stomach, 12 per minute in the duodenum and 8-9 per minute in the terminal ileon. Slow waves seem to be caused by an interaction between smooth muscle cells and ICCs. They do not elicit contractions, except in the stomach.
- Spike waves are generated automatically when the membrane potential in the resting smooth muscle exceeds -40 mV. They are 10-40 longer than neuron action potentials and are produced by calcium-sodium channels. Spike waves are real action potentials.

The resting membrane potential is around -56 mV, when it becomes more positive (i.e. less negative) membrane depolarization occurs and muscle fibres become more excited. When the potential becomes more negative, hyperpolarisation occurs and muscle fibres become less excitable. Parasympathetic nerves increase excitability by secreting acetylcholine, whereas sympathetic nerves decrease the excitability through the secretion of norepinephrine in its terminations.

During spike waves great quantities of calcium enter smooth muscle cells and most contractions are generated (Figure 12.5). Slow waves do not promote the entry of calcium ions (only sodium ions) into smooth muscle fibres and cannot produce muscle contraction.

Part of the muscle of the GIT produces tonic contractions, a state of permanent continuous semi-contraction of the muscle that is not associated with slow waves. They can last for several minutes or even several hours and may be caused by continuous repetitive spike potentials, hormones or other factors that induce membrane depolarisation (continuous entry of calcium ions into cells).

12.2. The mouth. Phases of swallowing

12.2.1 Cephalic phase

Before the food is ingested there are already changes in the digestive system to prepare for the different processes, such as absorption, digestion, etc. Thus, the sight of food and the anticipation of feeding stimulates the brain cortex, whereas food aromas stimulate the hypothalamus and the spinal cord. These stimuli produce an increase in salivary secretion, a contraction in the gallbladder and relaxation of the sphincter of Oddi, which implies a pancreatic secretion. 30% of gastric secretions are produced in the cephalic phase.

12.2.2 Oral phase

In this phase the food is already in contact with the gastrointestinal tract. The responses that occur in the oral cavity are the same as those initiated in the cephalic phase, plus the stimuli of taste, that involve a stimulation of the hypothalamus and spinal cord (Chapter 9). In this phase the food is crushed through the process of chewing, lubricated and mixed to form the bolus. Absorption in the oral phase is minimal, although alcohol and some drugs can be absorbed. The lubrication process is performed by the secretions of the salivary glands, that are formed by acinar and ductal cells. The former are secretory cells grouped in a spherical structure that release their contents towards the centre

of the acini (Figure 12.6). Ductal cells form the duct, that drains the salivary secretion from the glands into the mouth.

There are three main types of acinar cell: serous, mucinous and seromucous (mixed)

- Serous cells produce a watery secretion
- Mucinous cells produce a much thicker secretion
- Seromucous cells produce a mixed secretion

The proportion of serous, mucous and mixed cells varies in different salivary glands, the latter being found in the oral cavity and classified in minor glands, located in the oral mucosa and named based on their location (palatine, lingual, buccal and labial), and major glands (parotid, submandibular and sublingual). Each of them participates in the production of saliva in different percentages, thus, submandibular gland produces ~70%, parotid gland ~25%, and sublingual gland ~5% under baseline conditions. Saliva is secreted in the mouth in large quantities (1-1.5 l/day; 1 ml/minute/gram of gland). The composition of saliva (shown in Table 12.2) is determined by the biphasic model of salivary secretion:

- In phase 1 the cells of the acini and intercalar ducts produce a secretion with Na^+, K^+ and Cl^- concentrations close to those of plasma concentrations (135-145 mM, 3.5-5.5 mM and 115 mM, respectively).
- In phase 2 the concentration of solutes is modified while the primary secretion runs through the ducts: Na^+ and Cl^- are extracted and K^+ and HCO_3^- are added to the saliva, thus becoming hypotonic with respect to the plasma.

Salivary secretion is regulated by the autonomic nervous system through the salivary reflexes, that can be conditioned during the cephalic phase (aromas, food sight, noise of plates and cutlery, etc.), or unconditioned reflexes during the oral phase. Both types of reflexes stimulate salivary secretion.

12.2.3 Pharyngeal phase

Once the food bolus has formed, the tongue pushes it back and enters the pharynx, it is the so-called swallowing process, the process by which the bolus continues to the esophagus, a tube of approximately 25 centimetres that connect the pharynx with the stomach. The voluntary phase occurs once the food is prepared for swallowing, the tongue compresses the bolus against the palate and pushes it voluntarily towards the pharynx. After this phase the rest of the processes are involuntary:

- The palate is pulled upwards and palatopharyngeal folds move inward. This prevents food from going to the nasopharynx.
- Vocal cords are pushed and the pharynx moves forward and upward against the epiglottis. This prevents food from entering the trachea and helps to open the upper esophageal sphincter (UES).
- The superior pharyngeal constrictor muscles contract, thereby propelling the bolus into the pharynx.
- A peristaltic wave initiated by the contraction of the muscles pushes the bolus into the esophagus and relaxes the UES.

12.2.4 Esophageal phase

The main function is to quickly drive food from the esophagus to the stomach. The bolus passes through the UES to the esophagus in less than 1 second. The peristaltic wave that begins in the pharynx continues and spreads to the esophagus (primary peristalsis), then, a secondary peristalsis occurs as a result of esophageal distension, the lower esophageal sphincter (LES) relaxes and the bolus enters the stomach.

12.3 Stomach. Functional structure. Secretion. Postprandial activity and gastric motility.

The stomach has three layers of smooth muscle, the longitudinal, that continues in the duodenum, and the circular and the oblique, both ending in the pyloric sphincter. On the other, based on secretory, electrical and motor characteristics, the stomach can be divided into two functional regions (Figure 12.7):

- The proximal stomach, the anatomically coincides with the cardia, fundus and one third of the stomach body.
- The distal stomach, anatomically coincides with the antrum, two thirds of the body and the pylorus. The circular muscular layer is thicker in the antrum.

Glands differ depending on the region of the stomach, so that the gastric mucosa can be divided into three regions based on the structure of the glands:

- Glandular region of cardia, composed mainly of mucus-secreting cells

- Oxyntic or parietal glandular region composed of parietal cells, that secrete HCl and intrinsic factor (the protein that binds vitamin B_{12}), as well as enterochromaffin cells and D cells, which secrete histamine and somatostatin, respectively.
- Body region: Chief cells (secrete pepsinogen)
- Pyloric region: G cells (secrete gastrin)

12.3.1 Gastric secretion

Gastric juice is a mixture of secretions from specialised surface cells and cells of the gastric glands. Gastric juice, whose chemical composition is shown in Table 12.2, mixes with the bolus thus producing the chyme. Around 2-3 litres of gastric juice are secreted every day. The most important characteristic of gastric juice is its low pH (as low as 1) due to its high content in HCl. The stomach has approximately one billion parietal cells that secrete 0.16 M HCl. The parietal cell is highly specialized in this operation, that depends on active transport and, consequently, requires and enormous amount of ATP to be accomplished. The process of HCl production in parietal cells is shown in Figure 12.8. Some of the main functions of HCl are:

- Transformation of pepsinogen into active pepsin. Gastric pepsin is actually a heterogeneous set of proteins that are responsible for the proteolytic activity of gastric juice. These are secreted in the form of inactive zymogenic precursors called pepsinogen I (PGI) and pepsinogen II (PGII), two molecular variants that differ in net load and/or molecular weight (isozymes) (Figure 12.9). At pH 1.5 pepsin exhibits about 90% of maximum activity, decreasing to about 35% of maximum activity at pH 4.5.
- It facilitates the digestion of connective tissue and muscle fibres from ingested meat.
- It solubilises Ca^{2+} and $Fe^{2+/3+}$ salts, thus facilitating the absorption of these cations.
- It acts as a mechanism of defence by destroying bacteria.

Surface cells secrete bicarbonate (HCO_3^-), which is trapped by the mucus to form an alkaline viscous layer to protect the walls from acidity. The mucus is made up of glycoproteins, that are extremely hydrophilic and can form gels. There are two types of gastric mucus, visible and soluble. Visible mucus is made up of mucins (glycoproteins) that form a gelatinous coating with a high concentration of bicarbonate that protects the gastric epithelium from acid and pepsin. Mucin molecules are cross-linked by disuphide bridges which, along with the oligosaccharide chains, give the mucus a highly viscous consistency that easily expands upon hydration. Soluble mucus contains mucins without

disulphide bonds, therefore it has a less viscous consistency that allows the lubrication of the bolus and facilitates its mixing. Mucosal stability is increased by the presence of small peptides known as trefoil factors.

12.3.2 Gastric function: objectives

- Mechanical crushing of food
- Liquefaction of solids
- Digestion of macronutrients
- Maximal exposure of the products to enzymatic action
- Control of gastric emptying by regulating intestinal transit to a value of around 200 kcal/h (depending on whether it is solid or liquid, nutrients, etc.).
- Optimises pressure/volume ratio thus preventing gastroesophageal reflux and accelerating emptying
- Distention of the stomach wall generates important signals for the control of the posterior segments and gives a feeling of satiety.
- Preferential digestion of proteins, which requires a very acidic pH and a gastric mucosa protected by an alkaline mucus.
- Cleaning of residues and bacteria during the interdigestive phase.
- Acidity stimulates biliary and pancreatic secretions in the duodenum
- Unlike other nutrients, water and alcohol are absorbed in the stomach.

12.3.3 Regulation of gastric secretion

The regulation of gastric secretion is a true paradigm of gastrointestinal functioning as a whole and depends on an intricate balance of chemotransmitters with simultaneous excitatory and inhibitory actions. The regulation of gastric secretion is divided into three phases: cephalic, gastric and intestinal.

- Cephalic phase: Enteric neurons are activated via vagal route. These neurons release acetylcholine, that acts directly on parietal and enterochromaffin cells, and gastrin-releasing peptide (GRP) in the vicinity of G cells, that in turn release gastrin which activates parietal and chief cells.

- Gastric phase occurs when food has reached the stomach and causes the greatest generation of acid secretion of the three phases. The presence of food in the gastric lumen stimulates chemical and mechanical receptors, allowing amino acids and short chain peptides to stimulate the release of gastrin from G cells. Gastric distension triggers the release of acetylcholine and GRP.
- Intestinal phase occurs when the chyme reaches the duodenum.
    - Stimulation of the neuropeptide calcitonin gene-related peptide (CGRP) which acts on D cells to induce the release of somatostatin (decreases the release of gastrin and histamine).
    - In the duodenum, gastric acid is neutralised by sodium bicarbonate. This inhibits gastric enzymes, that have optimal activity at low pH values.
    - Local and hormonal reflexes cause the inhibition of the secretion mechanisms of HCl.

12.3.4 Gastric motility

Mixing, crushing and propulsion movements occur. Peristalsis begins minutes after the food has reached the pyloric part of the stomach, which is the one with the greatest muscle thickness and the greatest crushing power (Figure 12.10).

- During gastric filling, a weak peristaltic wave "A" begins at the antrum towards the pylorus. The gastric contents are compressed and pushed back towards the stomach body.
- A stronger “B” wave originates in the body and squeezes the gastric contents in both directions.
- The pylorus opens when wave "B" approaches and the duodenal bulb is filled. The “C” wave begins just above the incisure of the body.
- The pylorus closes again. Wave C fails to evacuate the content and a “D” wave starts higher in the body. The bulb can contract or remain full.
- Peristaltic waves are now originated higher in the body. Gastric content is intermittently evacuated.
- 3-4 hours later the stomach is almost empty. Small peristaltic waves empty the bulb with some reflux inside the stomach. There is antegrade and reverse peristalsis in the duodenum. Solid particles pass into the duodenum only if it is 0.3 mm or less in size, therefore the content is

practically liquid. Gastric emptying depends on the quantity and quality of chyme that the duodenum can process.

12.3.5 Regulation of gastric emptying

Gastric emptying is regulated by strong inhibition and weak facilitation.

- Strong inhibition by enterogastric reflex (that produces the contraction of pylorus and the inhibition of the propelling contractions of the antrum) and hormones, such as cholecystokinin, secretin, gastric inhibitor peptide (GIP), and somatostatin. The inhibition of gastric emptying triggered by the presence of the chyme in the duodenum is a function of its abundance, the presence of fat and protein degradation products, acidity of the chyme, hyperosmolarity, which implies contraction of the antrum and pylorus.
- Weak facilitation is triggered by gastric distension due to increased volume of the chyme in the antrum. Motilin, a peptide secreted in the interdigestive period, also accelerates gastric emptying.

12.4. Pancreas

Pancreas is divided into several parts: head, uncinate process, neck, body, and tail. The main pancreatic duct begins at the tail and ends in the lower portion of the head. It joins the bile duct forming the hepatopancreatic ampulla or ampulla of Vater, that terminates in the lumen of the duodenum. The accessory pancreatic duct begins in the cavity of the main duct itself, crosses the head of the pancreas and joins the duodenum through the Santorini's minor caruncle. It has no valves and can be considered as a simple way of derivation.

The pancreas is formed by exocrine and endocrine tissues. Exocrine tissue secretes digestive enzymes into a network of ducts that join the main pancreatic duct. Endocrine tissue, which is formed by the islets of Langerhans, secrete hormones into the bloodstream.

12.4.1 Physiology of exocrine pancreas

- The function of pancreatic acinar cells. The exocrine part is made up of epithelial (acinar and centroacinar) cells arranged in spherical or ovoid structures (pancreatic acini) formed by the

cells. The primary function of pancreatic acinar cells is the production of large amounts of enzymatic proteins that are stored as zymogen granules after being synthesised. Cells pour their contents into the luminal space of the acini by exocytosis. Cellular contents are subsequently transferred to the duodenum through the pancreatic ducts. Acinar cell are stimulated by acetylcholine, cholecystokinin (CKK), bombesin and substance P via membrane receptors that use inositol triphosphate (IP3) as a second messenger. Secretin and vasoactive intestinal peptide (VIP) stimulate acinar cells through adenyl cyclase. The aqueous component secreted by ductal cells is slightly hypertonic and presents a high concentration of HCO_3^-. As it progresses through the ducts, water is adjusted through the epithelium until the pancreatic juice becomes isotonic and part of the HCO_3^- is exchanged for Cl^- (Figure 12.11). Under resting conditions, the aqueous component is produced mainly in the intercalated ducts and other intralobular ducts. When the secretion is stimulated by secretin, the additional flow comes mainly from the extralobular ducts.

- Control of ionic secretion. More bicarbonate than chloride is secreted in the pancreatic duct, however, the situation is the opposite in the acini. Higher rates of secretion of pancreatic juice imply more production of bicarbonate and lower secretion of chloride, whereas concentrations of Na^+ and K^+ are maintained stable.
- Composition of pancreatic secretion. The pancreas secretes between 1.5 and 3 litres per day of an alkaline liquid (pH 8.1-8.5) that contains about 20 enzymes and proenzymes. HCO_3^- is the most important ion in pancreatic juice. Between 120 y 300 mmol/day are secreted daily. Its function is neutralise the acidic chyme that comes from the stomach, thus providing the adequate pH for pancreatic enzyme action (Table 12.2).

12.4.2. Physiology of exocrine pancreas

The endocrine pancreas is formed by the islets of Langerhans, which in turn are composed by different types of cells that secrete hormones directly into the blood:

- Alpha cells (α-cells) synthesise and secrete glucagon, a peptide hormone that increases the level of blood glucose (hyperglycemic hormone) by acting on different organs and tissues (Chapter 14).
- Beta cells (β-cells) produce and release insulin, a hypoglycemic hormone that regulates the level of glucose in the blood. Like glucagon, it exerts effects on multiple target organs and tissues (Chapter 14). Insulin is synthesised as "pre-proinsulin" and converted to "proinsulin"

in the endoplasmic reticulum. Pro-insulin generates equimolar amounts of insulin and C-peptide through the action of proteolytic enzymes. Insulin and the unfolded C-peptide are packed in secretory granules that accumulate in the cytosol of the β cell and are released simultaneously in response to glucose.

- Delta cells (δ-cells) synthesise somatostatin, a hormone that inhibits the contraction of both the smooth muscle of the digestive system and the gallbladder when digestion is over. It also inhibits the secretion of insulin and glucagon. Somatostatin secretion is regulated by high levels of glucose, amino acids and glucagon.
- PP cells or (gamma cells or F-cells) produce and release the pancreatic polypeptide (PP), that controls and regulates the exocrine secretion of the pancreas and contracts the gallbladder.

12.4.3 Regulation of exocrine secretion

Two periods can be distinguished in the exocrine pancreatic secretion: interdigestive and postprandial. During the interdigestive period pancreatic secretion is quite limited and considered to be under the control of nervous and hormonal mechanisms. Nerve regulation is performed mainly by the parasympathetic control, with enteropancreatic connections. The sympathetic nervous system influences by inhibiting interdigestive secretion and motility. The hormones with a greater role in this period are motilin and pancreatic polypeptide, which stimulate and inhibit secretion, respectively. Interdigestive regulation is considered important to clean the upper gastrointestinal tract of food particles, desquamated cells, and intestinal flora.

During the digestive period there is an increase of exocrine pancreatic secretion induced by hormonal and nervous stimuli triggered by food. Three phases are classically distinguished during this period: cephalic, gastric and intestinal. Pancreatic secretion must neutralise the acidic pH of the chyme, and thus the activity of gastric pepsin, that can damage the duodenal mucosa. On the other hand, a neutral pH is important to activate pancreatic enzymes and to increase the solubility of bile acids.

- Cephalic phase. The stimulation comes from the integration of stimuli such as chewing, smelling, or tasting. It is responsible for almost 50% of pancreatic secretion. Stimuli travel via the vagus nerve to acini and pancreatic ducts.
- Gastric phase: This phase is initiated by the gastric distension caused by the bolus and by the presence of amino acids and peptides in the stomach lumen. This stimulation activates efferent vagovagal reflexes and increases gastrin secretion. In this phase pancreatic enzymes are

preferentially secreted compared to water and bicarbonate. Its contribution to pancreatic secretion is less than 10% of total secretion.

- Intestinal phase: Pancreatic response is regulated primarily by the hormones secretin and CCK. The action of CCK is fundamentally paracrine, exerting its effect at the level of adjacent vagal fibres. The low pH in the chyme stimulates the production of secretin that, in addition to its endocrine action, also seems to act via paracrine route.

12.4.5 Summary of pancreas functions

The pancreas has digestive and hormonal functions:

- Enzymes secreted by the exocrine tissue of the pancreas participate in the digestion of carbohydrates, fats, proteins and nucleic acids in the duodenum. These enzymes are transported through the pancreatic duct to the bile duct as inactive zymogens, that are activated when they enter the duodenum. The exocrine tissue also secretes bicarbonate to neutralise the acid coming from the stomach to the duodenum.
- The main hormones secreted by the endocrine tissue of the pancreas are insulin and glucagon (which regulate glucose level in the blood and participate in energy homeostasis, as will be discussed in Chapter 14), as well as somatostatin.

12.5. The liver: structure. Hepatic secretion: storage and regulation.

The Couinaud classification divides the liver into eight independently functional segments, each of them having its own vascular flow, venous drainage and biliary drainage. In the centre of each segment there is a branch of the portal vein, the hepatic artery and the bile duct. On the periphery of each segment there is vascular outflow through the hepatic veins. 25% of the total blood passes through the liver.

At microscopic level, several structures are defined (Figure 12.12):

- Classic hepatic lobule. A morphological unit that has a hexagonal shape and is organised around the centrolobular vein. The interior consists of hepatocyte cords arranged radially around the centrolobular vein. Blood flows from the periphery to the centre of the lobule, into the centrolobular vein and bile flows to the periphery, into the bile ducts of the portal areas.

- Portal lobule. This unit is centred around the bile duct of the portal space and defined as the triangular area consisting of three hepatic lobules that are drained by the same bile duct of the portal space.
- Liver acinus. It has an approximate diamond shape and is formed by portions of two hepatic lobules irrigated by terminal branches of the portal vein and the hepatic artery.
- Hepatic sinusoids. They are a type of capillaries covered by a fenestrated (perforated) endothelium that separates hepatocytes from blood cells. They allow the passage of blood plasma in the space between hepatocytes and the endothelium. The blood filtered through the sinusoids, comes directly from the stomach and intestines. Sinusoids also contain phagocytic cells (hepatic macrophages or Kupffer cells), which eliminate bacteria and wastes from the blood. Around the sinusoid, there are Ito cells or lipocytes, that store vitamin A and lipids.

After a meal the hepatocytes:

- Absorb glucose, amino acids, iron cations, vitamins and other nutrients in order to be metabolised or stored.
- Eliminate and degrade hormones, toxins, bile pigments and drugs.
- Secrete albumin, lipoproteins, coagulation factors, angiotensinogens and other products in the blood.

During the periods between meals hepatocytes release glucose in the circulation.

The hepatic artery, which carries oxygen-rich blood into the liver, arises from the aorta, the largest artery in the body. Arteries from the aorta also give rise to the capillaries that capture nutrients from the intestine and converge in the portal vein, which enters the liver. Within the liver, the branch of the hepatic portal vein and the hepatic arteries join in the spaces between the hepatic lobes, all of them draining into the hepatic sinusoids. Therefore, there is an unusual mixture of venous and arterial blood in the sinusoids.

Substances are exchanged in the liver and blood subsequently passes to the hepatic vein, which flows directly into the vena cava, that delivers it to the heart. During interdigestive periods bile is stored in the gallbladder

12.5.1 Bile production by the hepatocytes

Hepatocytes secrete conjugated bile acids (bile salts), conjugated bilirubin, ions and water into the bile canaliculi that terminate in the bile ducts, where bicarbonate is secreted through the action of hormones and vagal stimulation. The bile that goes through the bile ducts is an alkaline aqueous secretion that is stored in the gallbladder. Bile is a green, bitter-tasting liquid substance produced by the liver. It is involved in digestion processes functioning as an emulsifier of fatty acids.

12.5.2 Synthesis of bile acids.

Bile acids are synthesised in the liver from cholesterol by two different pathways. The primary bile acids are cholic acid (Chapter 4) and chenodeoxycholic acid.

Approximately 90-95% of bile salts (sodium and potassium salts of bile acids) are reabsorbed in the ileum, while 5-10% pass to the colon where they are modified through bacterial action, thus producing secondary bile acids. These are partially reabsorbed (some are lost in the faeces) and return to the liver to be conjugated with glycine or taurine. This process produces glycocholate, taurocholate, glycokenodeoxylate and taurochenodeoxycholate. New bile acids are only synthesised by the liver to replenish faecal losses.

Bile salts discharged into the duodenum are absorbed in the ileum by co-transport with sodium, delivered to the liver via portal vein, and returned to the intestine with the bile. This recirculation occurs several times a day (enterohepatic recirculation).

12.5.3 Regulation of liver secretion and vesicular emptying

- Bile secretion. The substances that increase bile secretion are known as choleretics. The vagus nerve releases acetylcholine, that activates bile secretion. At the same time, bile salts stimulate secretin release, that increases the secretion of bile and bicarbonate in the duodenum (Figure 12.13).
- Biliary emptying. Cholagogues stimulate vesicular emptying. The vagus nerve elicits a weak stimulation of vesicular contraction, while hormonal control by CCK produces a potent contraction of the gallbladder that pours bile into the duodenum in response to the presence of food (Figure 12.13).

Bile is stored and concentrated in the gallbladder for several hours. Concentration is achieved by active reabsorption of Na^+, followed by passive reabsorption of Cl^- and water (Ca^{2+} is not reabsorbed).

The concentrations of solutes and bile salts are therefore higher in stored bile (and with a slightly lower pH) than in the bile flowing through the hepatic duct. Bile can be concentrated 5 to 20 times.

12.4.4 Functions of bile salts

Bile salts are amphipathic: they have a hydrophilic polar groups and a hydrophobic apolar nucleus (the cyclopenta[α]-phenanthrene carbon skeleton, see Chapter 4). The main functions of bile salts are:

- Upon reaching a certain critical level of concentration, bile salts associate to form micelles with their hydrophilic part facing outward and the hydrophobic part inward. These micelles interact with the digested lipids present in the intestinal lumen, thus forming mixed micelles, that deliver the lipids to the brush border of the enterocytes for absorption (Chapter 13).
- Bile salts alkalise the duodenum, along with pancreatic secretion and intestinal juice.
- They are an excretion route for some waste products: bile pigments, steroids and cholesterol, heavy metals and drugs.

12.4.5 Liver functions (discussed in Chapter 14, section 14.6)

12.5 Small intestine

The basic structure and the specialised cells of the small intestine are described in Chapter 13

12.5.2 Digestion in the small intestine

12.5.2.1 Chemical digestion

Bile and pancreatic juice are poured into the duodenum, which act on the chyme in the lumen of the intestine and form the chyle. The function of pancreatic juice is to provide enzymes that degrade carbohydrates, fats and proteins. Intestinal juices contain enzymes that continue with the degradation of carbohydrates and proteins (Table 12.2), while bile emulsifies fats. This phase of intestinal chemical digestion, which takes place in the lumen of the organ, is known as luminal digestion.

12.5.2.2 Mechanical digestion: Motility

Motility in the small intestine varies depending on the gastric phase:

- During the interdigestive phase, the pattern of motility is described by the so-called "migrating motor complex" (MMC) or migratory myoelectric complex, that consists of three phases:
    - Phase I lasts about 70 minutes. During this phase, only the basic electric rhythm and hydro-saline secretion can be observed.
    - Phase II lasts between 10 and 20 minutes and is characterised by a slight increase in base activity, with intermittent irregular low-amplitude contractions, along with secretion acidic and enzymatic.
    - Phase III is the motor activity phase, that presents contraction waves at a rate of 11 to 13 per minute with a duration of 1 to 5 minutes. The duration of these phases varies between individuals and even in the same individual depending on the time of day.

  MMC takes about 90 minutes to travel the entire intestinal tube and ends upon reaching the ileocecal valve, then a new motor complex is generated in the stomach. This process is associated with two functions: secretion, during phase I and II, and propulsion, during phase III. The latter eliminates intestinal waste that might cause the growth of harmful bacterial. It has also been shown that some absorption occurs during phase I and II. The main hormonal regulator of MMC is motilin.
- During the digestive phase the presence of circulating gastrin, cholecystokinin (CCK) and neurotensin, adapt gut motility to a digestive pattern, characterised by a segmental and random motor activity dependent on neurohormonal influences. MMC is inhibited during a variable period of time that depends on the caloric intake and on the type of nutrient, so that fats delay MMC more than carbohydrates and the latter more than proteins. The digestive pattern shows two types of movement:
    - Segmentation movements are characterised by close contractions of the circular muscular layer, dividing different segments of the intestine into small portions that give a characteristic image of "string of sausages". Segmentations are rhythmic, with a frequency of 7 to 12 times per minute, and are produced in such a way that each time the segmentation originates at a different point. These movements allow the chyme to mix with secretions and promotes absorption of nutrients (Figure 12.14).

- Propulsion movements are produced by peristalsis: a contraction is followed by a relaxation of the circular muscle, which propagates in the distal direction. Contractions occur randomly at different points of the small intestine and their propagation affects segments of different lengths. This causes a very slow propulsion of the intestinal contents (1 to 2 cm/s).

In certain circumstances where the mucosa is threatened by mechanical or chemical damage, an intense peristaltic contraction is generated at the point of damage that quickly crosses the entire intestinal tube, in both directions (oral and caudal) from the point of origin. This movement is known as peristaltic rush and its function is to quickly evacuate the harmful contents of the intestine.

Another movement in the intestine involves irregular contractions of muscular layer of the mucosa at a frequency of 3 contractions per minute. This movement is under the tonic activation of the sympathetic nervous system and other chemical stimuli and leads, on the one hand, to the formation of the characteristic folds of the mucosa and, on the other, to a periodic shortening and lengthening of the intestinal villi that favours blood and lymphatic drainage.

12.5.2.3 Regulation of small intestine motility

A number of reflexes control the number, frequency and strength of peristaltic waves. Among the most relevant are:

- Gastrointestinal reflex. The presence of food in the stomach leads to an increase in intestinal motility.
- Intestino-intestinal reflex. The presence of chyme in the intestine increases intestinal motility.
- Gastroileal reflex. The presence of food in the stomach increases motility especially at the level of the ileum in order to facilitate its emptying.
- Parasympathetic nervous system. An increase in parasympathetic stimulation increases intestinal motility.

12.5.3. Composition of intestinal secretions

The cells that line the internal surface of the small intestine release a mixture of substances known as intestinal juice, that includes water, bicarbonate, mucin, mineral salts and a variety of enzymes, (Table

12.2). The intestinal juice has an alkaline pH to counteract the acidity of chyme and continues the digestion of macronutrients along the small intestine.

12.5.4. Small bowel emptying

Intestinal emptying occurs through the ileocaecal valve, which is contracted under basal and unstimulated conditions, generating a high pressure area and preventing the passage of the ileal content to the caecum. This optimises nutrient uptake by the ileal mucosa. The ileocaecal valve appears to relax only when the peristaltic waves of the ileum reach it, thus causing a small spill of chyme in the caecum, whose distension causes a reflex contraction of the sphincter. This response is fundamentally nervous, so that both the vagus nerve and the sympathetic nervous system stimulate sphincter contraction. Acetylcholine is the vagal mediator and norepinephrine is the sympathetic mediator. Gastrin may also participate in this response because it stimulates the motility of the ileum and the relaxation of the sphincter. The gastroileal reflex causes an increase of the motility of the ileum and, consequently, of ileocaecal evacuation. Normal bowel emptying is about 1500 ml/day. Overall, the functions of the ileocaecal valve are:

- Avoid caecum overload.
- Increase the residence time of the chyme in the ileum, favouring absorption.
- Increase the residence time of the chyme in the large intestine, favouring the reabsorption of water and electrolytes, as well as bacterial action (see below).

12.5.6 Functions of the small intestine

- Motor function. It allows cleaning movements during the interdigestive periods and food mixing and kneading in the digestive phase, thus facilitating nutrients absorption.
- Secretory function. The highest proportion of intestinal secretion comes from exocrine pancreatic secretion and biliary secretion, which are poured into the duodenum through the sphincter of Oddi. The mucosa of the small intestine also secretes some digestive enzymes, the most important being enterokinase, that activates the pepsinogen secreted by the pancreas.
- Digestive function. The intestinal mucosa contains its own enzymes at the luminal surface in addition to those from the pancreatic exocrine secretion, which are responsible for the final digestion of the chyme. Some intracellular digestion also occurs.

- Absorption function. The intestinal mucosa is designed to perform the absorption of most of the nutrients (Chapter 13).
- Endocrine function. A high number of hormones are produced and secreted in the small intestine, all of them aimed at regulating intestinal digestion and absorption. To accomplish this task, there is a set of chemical and mechanical receptors whose stimuli trigger specific hormonal responses. A number of reflexes are also involved.
- Protective function. This function is determined by the basicity of intestinal secretions and by a powerful immune barrier.

13.7. Large intestine. Functional structure. Absorption and secretion. Motility of the colon: peristalsis and mass movements. Defecation

The large intestine is 1.5 metres long and extends from the ileocecal valve to the anus. It consists of the caecum, the appendix, the colon, the rectum and the anal canal. The colon is in turn divided into ascending colon, transverse colon, descending colon and sigmoid (or ileo-pelvic) colon.

The longitudinal muscle of the large intestine does not form a continuous layer, but is divided into longitudinal bands, or teniae. Since these bands are shorter than the circular muscular layer, they cause the formation of folds (haustras) in the wall of the large intestine.

The rectum is the last portion of the digestive system, being located between the sigmoid colon and the anus. It has an approximate length of 20 cm. The function of the rectum is to store the stool before being expelled through the anal opening. The rectum extends to the anus, an opening that has an internal sphincter of smooth muscle cells and an external sphincter of striated muscle.

The colon contains numerous straight tubular glands with goblet, regenerative and enteroendocrine cells. The lining cells, the colonocytes, are specialised in the absorption of water, some vitamins, and electrolytes.

13.7.1 Motility of the colon

- Mixing or segmentation movements. They are tonic waves of contraction that move back and forth (also called antiperistaltic waves). They occur with a frequency of 3 or 4 per minute and allow prolonged contact of the intestinal contents with the mucosa.
- Propulsion movements or mass movements occur from the transverse colon to the sigmoid. They are a type of modified peristalsis: a constriction ring appears, then, 20 cm or more of

the colon loses the haustrations, contracting as a unit, and pushing the stool forward. This type of movement usually occurs a few times a day (1-3), especially within the hour after breakfast and lasts for 10 to 30 minutes. When the stool reaches the rectum, the desire to defecate appears.

Mass movements are regulated by the gastro-colic reflex (when food enters the stomach) and duodeno-colic reflex (when food penetrates into the duodenum), thus favouring the occurrence of mass movements after meals.

12.7.2 Chemical digestion in the large intestine.

Goblet cells, very abundant in the lining epithelium of the colon, secrete mucus. The purpose of this secretion is to lubricate and confer an appropriate consistency to faeces, while its alkaline pH is neutralises and protects the intestinal mucosa. The final stage of digestion in the colon is performed by bacteria (Figure 12.15)

12.7.3 The rectum

The rectum is normally empty because the intestinal content reaches the sigmoid colon and rectum only when mass movement occurs. This situation leads to the distention of the walls, thus triggering the defecation reflex. The rectum can also retain faecal content for a short period of time

At rest, the anal canal is closed by an internal anal sphincter (involuntary tonic contraction), that acts as a first barrier, and the external anal sphincter and the puborectalis muscle (tonic contraction under voluntary control), that act as a second barrier.

When a mass movement forces stool into the rectum, a person feels like defecating.

- Afferent signals that propagate through the myenteric plexus increase peristalsis towards the rectum, driving stool towards the anus and relaxing the sphincter.
- If nerve endings of the rectum are stimulated, signals are transmitted to the spinal cord and through the parasympathetic fibres of the pelvic nerves, then, signals return to the descending colon, sigma, rectum and anus, increasing peristalsis and relaxing the sphincter.
- Acetylcholine and substance P produce stimulation
- Norepinephrine and peptide Y increase anal pressure
- The sympathetic nervous system is responsible for the contraction

12.7.4 Defecation reflex

The following sequence of events is established under the influence of the parasympathetic nervous system:

1- Peristaltic contraction of the end of the colon and rectum.
2- Contraction of the musculature of the pelvic floor.
3- Relaxation of the anal sphincters.

The reflex is usually accompanied by a strong inspiration, closure of the glottis to prevent air outflow, and contraction of the abdominal and thoracic muscles, that results in an increase in intra-abdominal and intra-thoracic pressure.

12.7.5 Faeces composition

- Water: 70-80%
- Solid waste (20-30%), composed of undigested food residues, such as dietary fibre (cellulose, lignin), cellular and bacterial debris, bile compounds (stercobilin, responsible for their colour), enzymes and gases.
- Faecal fats: about 5% of ingested fats (6 grams/day)
- Faecal nitrogen: 1.4-1.7% of ingested protein (1-2 grams/day)

12.7.6 Functions of the large intestine

- Reabsorption of water, vitamins and some electrolytes
- Disposal of waste substances
- Bacteria of the large intestine also make some important substances, such as vitamin K.

12.8. The microbiota of the gastrointestinal tract and its functions

The gastrointestinal microbiota (formerly known as flora) is formed by a large group of more than 100 trillion (10^{14}) bacteria of more than 400 species that live in the digestive system (archaea, viruses, and fungi are also present). These microorganisms are found from the mouth to the final part of the

large intestine. From the esophagus, practically aseptic, the microflora presents a gradient in quantity and variety, being scarce in the stomach and gradually increasing from the small intestine and into the colon, where it performs its main functions:

- Probiotic effect (maintenance of intestinal balance), acting as a barrier for the entry of germs and pathogens that arrive with food. This is accomplished by:
    - Competition with pathogens for nutrients and adhesion sites in the mucosa.
    - Generation of a hostile environment for pathogens.
    - Activation of the immune system.
- Energy production from non-digestible fibre
- Synthesis of vitamin K and some vitamins of B group (biotin, cobalamin, folates, nicotinic acid, pantothenic acid, pyridoxine, riboflavin, and thiamine)
- Participation in the absorption of calcium, magnesium, sodium and (partially) iron

LEGENDS TO FIGURES

Figure 12.1. Simplified general scheme of the digestion process.

Figura 12.2. Gastrointestinal wall. Longitudinal and transverse section (Valls-Belles, V.)

Figure 12.3. Submucosal plexus and myenteric plexus (Valls-Bellés, V.)

Figure 12.4. Membrane potential across the membranes of smooth muscle cells of the gastrointestinal tract (?)

Figure 12.5. Action potentials at the membranes of smooth muscle cells (adapted by Valls-Belles from ?)

Figure 12.6. Structural organization of salivary glands (downloaded from https://www.intechopen.com/books/histology/salivary-glands)

Figure 12.7. Schematic representation of the structure of the stomach

Figure 12.8. Production of hydrochloric acid (HCl) in parietal (oxyntic) cells

Figure 12.9. Activation of pepsin from pepsinogen in the presence of hydrochloric acid (HCl)

Figure 12.10. Gastric motility

Figure 12.11. Structure of exocrine pancreas and function of pancreatic acinar cells (Adapted by JRPC from Koeppen and Stanton. Berne and Levy Physiology. Sixth edition)

Figure 12.12. Schematic representation of the hepatic lobule (Valls-Bellés)

Figure 12.13. Schematic representation of the regulation of bile secretion and gallbladder emptying.

Figure 12.14. Propulsion and segmentation movements in the small intestine. Departamento de Fisiología, Escuela de Medicina, Universidad de Costa Rica 2007, Autor del Contenido y Actividades: Dr. Luis Fernando Pacheco B. Administrador Web: Ing. Arlyne Solano G. asolanog@cariari.ucr.ac.cr

Figure 12.15. Final stages of digestion by gut microbiota

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