Secretory functions of the gastrointestinal tract

Henrik Isackson

Christopher C Ashley

Abstract

The intestine is an organ of functional diversity. The absorption of water, nutrients, minerals, and vitamins is made possible through the coordinated action of the intestine, stomach, exocrine pancreas and hepatobiliary system.

Keywords GI-tract; secretory mechanisms; luminal nutrient sensing; gastric secretion; regulation

Introduction

As food stuff passes through the alimentary canal it is manipulated through mechanisms controlled via endocrine, paracrine, and neural elements. The cephalic phase of digestion is mainly under neural control mechanisms whereas hormonal mechanisms dominate the gastric and intestinal. The process whereby the release of such hormones is controlled is termed luminal nutrient sensing (LNS; Figure 1).

Luminal nutrient sensing

Amino acids have shown to stimulate glucagon-like peptide-1 (GLP-1) secretion from gut L-cells, although their potency is lower than that of glucose and fat. Fatty acids are potent stimuli for both glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 secretion. The digestion of triglycerides to fatty acids is crucial as pancreatic lipase inhibition reduces the GIP and GLP-1 response seen from fat ingestion. Suggested effects from bile acids come from experiments with perfused explanted rat colon, in which increasing the luminal presence of bile acids increases the concentration of GLP-1 in the portal venous effluent. The G-protein coupled bile acid receptor-1 (GPBAR1), was found highly expressed in mouse colonic L-cells. High fat diet in Gq-protein coupled free fatty acid receptors (GPR40)-null mice fails to induce an increase in plasma GIP and GLP-1 levels.[1,2]

Gastric secretions

Most secretory cells in the stomach mucosa are situated in gastric pits. These comprise oxyntic (parietal) cells secreting parietal juice of pH as low as 2.0, mucous secreting columnar and neck cells, and pepsinogen secreting chief cells. Secretory cells in the epithelium also secrete HCO_3^- protecting the mucosa from the luminal HCl (Figure 2A).

The parietal cells secrete the intrinsic factor (IF). IF is a 55 kDa glycoprotein complexing with vitamin B12 facilitating ileal B12 absorption. Surgical resection of the fundus or gastritis can leave the patient dependent on lifelong parenteral supply of B12 to avoid deficiency-related anaemia and neuropathy.

Mucus is mainly secreted from columnar epithelium through exocytosis or desquamation of epithelial surface cells during churning, but also from the mucous neck cells upon vagal stimulation. Pyloric glands contain mucus-secreting cells identical to the mucous neck cells. The mucus layer of the stomach is 80–280 μm thick and made up from mucins, a tetramer glycoprotein family protected from pepsin digestion by long galactose and N-acetyl glucosamine chains, but also small amounts of nucleic acid, lipids, and other proteins including immunoglobulin, all suspended in an alkaline saline. HCO_3^- is secreted from non-parietal epithelial cells. The small HCO_3^- confining volume enables the pH at the epithelial membrane to be neutral whereas the stomach lumen pH ~ 2.0.[4]

Pepsinogen is the 42.5 kDa precursor of pepsin. It exists in two isoforms: pepsinogen I and II. Storage as inactive precursors prevents autodigestion of the stomach mucosa.[4] Pepsinogen I is released through exocytosis from chief cells in the oxyntic glandular stomach area and pepsinogen II from mucous and glandular cells in the oxyntic and pyloric mucosa.[5] 35 kDa pepsin I is formed through acid-dependent pepsinogen I hydrolysis. Pepsin I degrades about 20% of ingested protein and is especially important due to its ability to digest collagen in meat products. Gastric acid establishes the optimum working pH range for pepsin: 1.8–3.5. Pepsin denatures at pH > 5.

Regulation of gastric secretion

Gastrin, acetylcholine (Ach), and histamine are major stimulants of gastric secretion via independent G-coupled receptors on oxyntic cells. 80% of gastrin is secreted from G-cells in the pyloric antrum mucosa and duodenum. It exists in two main isoforms: G34 (34 amino acids) and G17. 90% of gastrin present in the antral mucosa is G17. This indicates that G17's main site of action is the stomach mucosa. Gastrin is also produced in the pancreas and is a diverse player in GI-regulation; involved in parietal cell HCl secretion and maturation, promoting pepsinogen secretion, stomach contractions, and constriction of the lower oesophageal sphincter (LOS).

Stomach lumen gastrin promotes histamine release from enterochromaffin-like (ECL) cells via cholecystokinin-2 (CCK-2) receptor, but also acts directly on the parietal cell CCK-2 receptors causing apical membrane H^+/K^+-ATPase translocation.[5] Gastrin and CCK share the same five C-terminal amino acid residues.

Vagal action releases Ach and gastrin-releasing peptide (GRP) to induce gastric acid secretion. There is little evidence from 'sham-feeding' in man of cephalic phase-gastrin release. However, gastric phase distension of the stomach wall induces gastrin release from wall neurons. Ach acts directly on parietal cell M_3 receptors causing acid secretion. It also facilitates HCl secretion by inhibiting inhibitory somatostatin release from antral D-cells. GRP is released from vagal neurons stimulating G-cells to gastrin secretion.[5] Histamine H_2 blockers, such as cimetidine, block the action of histamine on the oxyntic cells, and acid release by Ach and gastrin, illustrating histamine's key role in these events. The

Henrik Isackson ***MD*** *received his clinical training from Lund University and is currently doing doctoral work at the Department of Cardiovascular Medicine, University of Oxford, Oxford, UK. Conflicts of interest: none declared.*

Christopher C Ashley ***DSc (Oxon) Hon MRCP FMedSci*** *is a Professor and Medical Tutor Emeritus at Corpus Christi College, University of Oxford, Oxford, UK. Conflicts of interest: none declared.*

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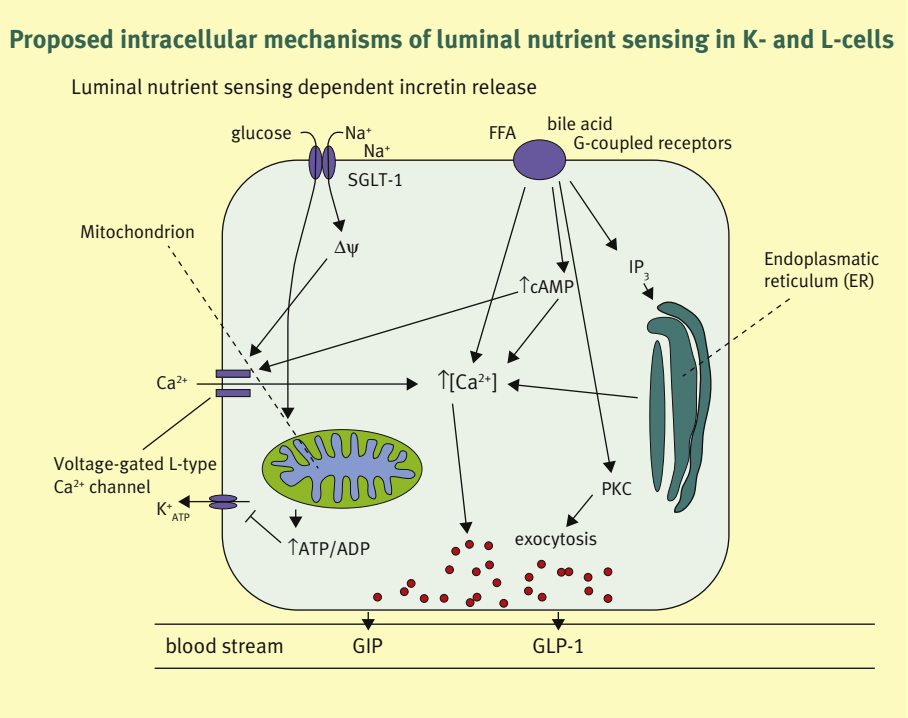

Figure 1 Secretion of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) through exocytosis is dependent on a rise in $[Ca^{2+}]_i$. Glucose is absorbed through sodium-coupled glucose transporters (SGLT-1). The rise in $[glucose]_i$ increases the ATP level which inhibits the activity of the ATP-sensitive K^+ channel (K^+-ATP). Na^+ influx as well as decreased K^+ efflux depolarizes the cell membrane which increases the opening probability of the voltage sensitive L-type Ca^{2+} channels, causing an influx of Ca^{2+}. Free fatty acids (FFA) and bile acids bind G-protein coupled receptors which activate intracellular pathways raising levels of cyclic adenosine monophosphate (cAMP). Their downstream activating pathways cause a rise in cAMP which results in increased opening probability of voltage gated Ca^{2+} channels, and also protein kinase C (PKC) and inositol(1,4,5)-trisphosphate (IP3) causing Ca^{2+}-release from intracellular stores to initiate exocytosis.[1,2]

H^+/K^+-ATPase inhibitor omeprazole is also highly effective at controlling acid production by the parietal cell.

Histamine is secreted from ECL cells deep in the gastric pits closely associated with parietal cells. It works in a paracrine fashion stimulating HCl secretion via parietal cell H_2 receptors and induces translocation of H^+/K^+-ATPase to the apical membrane via increased $[cAMP]_i$. Histamine secretion is mainly induced by gastrin.[5]

Pepsinogen secretion is induced by substances including Ach, CCK, gastrin, and secretin. Ach is regarded as the most potent inducer through the association with M_3 receptors causing activation of phospholipase C (PLC) and increased $[Ca^{2+}]_i$.[6]

Somatostatin is the main inhibitor of HCl secretion. It is released from δ-cells throughout the gut mucosa as well as in the endocrine pancreas, and from submucosal and myenteric neurons. Gastric release is mainly from antral and fundal cells in close proximity to parietal, ECL, and G-cells. The release is stimulated by acid, free fatty acids (FFA), glucose and distension. Somatostatin acts directly on parietal cells and indirectly by inhibiting histamine and gastrin release.[7]

Secretions from the intestinal wall

Brunner's glands, found in the proximal duodenum, secrete alkaline mucus to lubricate chyme and protect the duodenal wall from digestion by gastric acid. Mucus is also secreted from goblet cells in the crypts of Lieberkühn along the whole intestine, the stomach excluded.

Luminal gastric acid stimulates HCO_3^- secretion from secretory cells in the proximal duodenum neutralizing gastric acid (Figure 2B).

Mucus formation is a process of mucin exocytosis from goblet cells throughout the intestinal epithelium. In intracellular vesicles these are associated with Ca^{2+} and H^+. Dissociation of these ions is important in the protein's expansion and formation of luminal mucus. The process is probably aided by the enterocyte secretion of HCO_3^-. This has been proposed as a mechanism underlying the highly viscous mucus in cystic fibrosis (CF), the primary phenotype of the disease of dysfunctional cystic fibrosis transductance regulator (CFTR) where a local deficiency of HCO_3^- contributes to increased mucus viscosity.[8] For nutrients to reach the absorptive enterocyte villi, they have to move through the mucus. In coeliac disease, where a cross-reaction towards tissue protein is initiated by an immunological response towards gliadin in wheat, villus atrophy occurs causing reduced stirring and transport of nutrients across the mucosa to the epithelium brush border, adding to an already reduced absorptive capacity. The result is reduced absorption of fats causing steatorrhoea, weight loss, reduced absorption of fat soluble vitamins A, D, E, and K, and anaemia due to iron, folic acid and B12 malabsorption. Gluten-free diet restores absorptive capacity.

Regulation of small intestine secretion

Neurotransmitters Ach and vasoactive intestinal polypeptide (VIP) stimulate HCO_3^- secretion together with luminal

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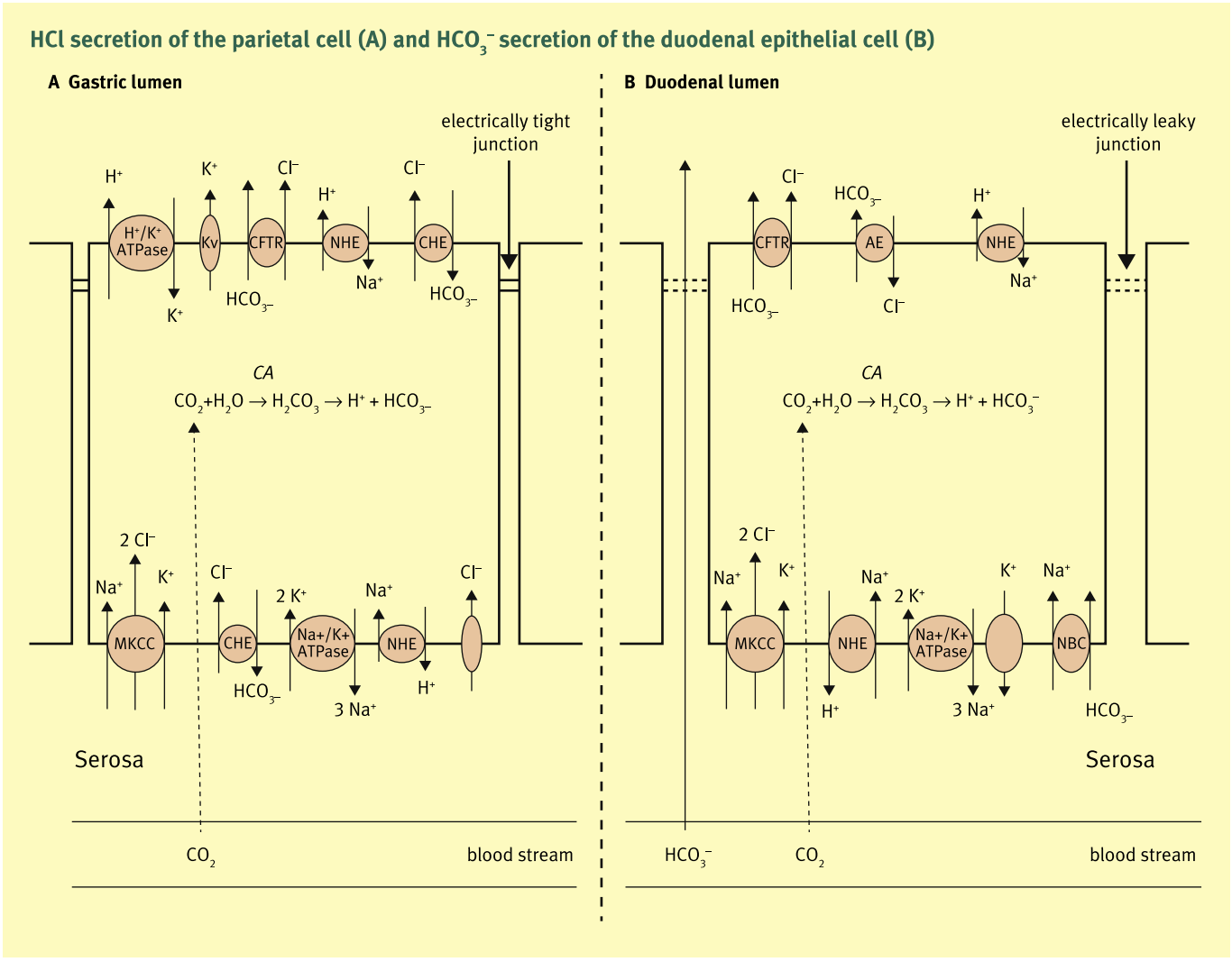

Figure 2 A: ATP-dependent H^+/K^+-exchange, Cl^- extrusion, and K^+ recycling, are central for HCl secretion. H^+ is derived from H_2CO_3 which forms from H_2O and CO_2 under the influence of carbonic anhydrase (CA). The H^+/K^+-ATPase is the major H^+-extruder consuming approximately 1500 calories per litre of secreted gastric juice generating a 10^6 times concentration gradient over the apical membrane. It is effectively inhibited by omeprazole. The Na^+/H^+ exchange (NHE) transporter in the apical membrane transports Na^+ down its concentration gradient in exchange for H^+.[3] Together with the Cl^-/HCO_3^- exchange (CHE)-transporter the cystic fibrosis transductance regulator (CFTR) promotes the transport of Cl^- against its electrochemical gradient into the stomach lumen. The voltage gated K^+ channel (Kv) is required to sustain the action of the H^+/K^+-ATPase. HCO_3^- is secreted basolaterally down a concentration gradient into the blood, in exchange for Cl^-. The NHE of the basolateral membrane also helps to regulate pH. The NKCC conveys the electroneutral inward transport of one Na^+, one K^+, and two Cl^-. Cl^- also passes down its concentration gradient via exclusive Cl^--channels. Na^+/K^+-ATPase generates the electrochemical gradient of Na^+ and K^+. Tight junctions in the gastric epithelium are electrically tight, preventing paracellular ion diffusion. **B**: In the duodenal epithelial cell apart from paracellular access of HCO_3^- from the blood to the duodenal lumen over leaky tight junctions, there are facilitating transport mechanisms over the apical membrane together with Cl^-. Cl^--transport also occurs through the CFTR.[4] An electroneutral NHE prevents intracellular pH decrease. Processes supporting the apical export of HCO_3^- include the NKCC, NHE, the Na^+/K^+ pump, a Na^+/HCO_3^- co-transporter (NBC), and an outward exclusive K^+ channel.

prostaglandin E_2 (PGE_2). Ach acts via an increase in $[Ca^{2+}]_i$, and PGE_2 and VIP act via G-protein coupled receptor activation, raising $[cAMP]_i$. Stimulatory factors include luminal acid, glucose, and bile salts, but also wall distension. Stretch reflexes involve the parasympathetic as well as intrinsic enteric nervous system. The sympathetic neurotransmitters noradrenaline (NA) and neuropeptide Y (NPY) inhibit secretion. Somatostatin in the duodenal wall works as a neurohormonal inhibitor released from enteric nerve endings. It acts directly on crypt cells by decreasing $[cAMP]_i$ levels via a G-protein coupled receptor (SSTR1).[4] Mucin release is closely associated with that of HCO_3^- through the CFTR, and is stimulated by PGE_2 and serotonin.[9] The cholera toxin enters secretory cells through receptor-mediated endocytosis causing permanent activation of G-protein receptors elevating $[cAMP]_i$, activating the CFTR, and increasing Cl^- and associated Na^+ secretion with watery diarrhoea as a result. Excessive loss of HCO_3^- generates metabolic acidosis.

Pancreatic exocrine secretion

Pancreatic exocrine secretion contains digestive enzymes and alkaline saline. Electrolytes are secreted from ductal and

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centroacinar cells whereas enzymes originate from acinar cells at the terminal end of the secretory units. HCO_3^- protects the duodenal mucosa from acid and establishes an optimal pH for digestive enzymes, and facilitates micelle formation, a process described below. The pancreatic juice, as it enters the duodenum, holds a pH of 7.4–8.3 contributing to the settling of duodenal chyme at approximately pH 7, inactivating pepsin. HCO_3^- is secreted to the pancreatic duct lumen in analogy with the duodenal secretory process. Protons from H_2CO_3 dissociation are transported across the basolateral membrane making the postprandial pancreatic effluent slightly acidic reducing the effect of the stomach alkaline tide. The electrolyte fluid also contains Na^+, and K^+ which travels via the paracellular route down the electric gradient increasing water flow through osmotic mechanisms. With increased flow the secretion entering the duodenum becomes similar to the primary pancreatic composition due to reduced ductal cell modification. Cl^- stands in reciprocal relationship with HCO_3^- due to antitransport in the CFTR channel of the apical membrane. Hence, with an increase in flow $[HCO_3^-]$ increases due to decreased reuptake, whereas $[Cl^-]$ is reduced as less is secreted.

Proteolytic enzymes are stored in intracellular zymogen granules in the terminal acinar cells of the secretory lobules and secreted as inactive precursors to avoid pancreatic tissue autodigestion. Trypsin and chymotrypsin have a strict endopeptidase cleavage pattern whereas carboxypolypeptidase releases single amino acids from the carboxyterminal end of proteins reducing polypeptides to single amino acids. The trypsin precursor trypsinogen is initially activated by enterokinase, situated on the intestinal epithelium brush border. Activating trypsinogen causes an autoactivation cascade which if it occurs in the pancreas causes tissue autodigestion. To prevent premature activation pancreatic juice contains pancreatic secretory trypsin inhibitor (PSTI). Trypsin also activates other enzyme precursors in the duodenal lumen. Elastase is the only enzyme which is capable of degrading connective tissue elastin.

Postnatally intestinal cells can absorb protein by endocytosis, a process designed to transfer passive immunity from the mother. Even adult intestines can absorb small amounts of protein and polypeptide. Although the majority of protein is absorbed eventually via specific amino acid co-transporter systems and defects in these systems are responsible for Hartnup disease and cystinuria, the enterocyte can absorb di-, tri-, and tetra-peptides, these being subsequently intracellularly hydrolysed. The transporter for this process is the oligopeptide transporter (PepT1) which is effective at transporting multiple amino acids, rather than a single amino acid, and is dependent upon H^+ inward co-transport.

Pancreatic α-amylase, the main carbohydrate-degrading enzyme, hydrolyses sugars, starch, and glycogen to glucose and disaccharides. Pancreatic lipase is dependent on a coenzyme, pancreatic colipase, in order to reach full activity as this counteracts biliary acids' inhibitory effects on pancreatic lipase. Pancreatic lipase hydrolyses triglycerides, forming FFA and monoglycerides. Cholesterol esterase hydrolyses ester linkages between fatty acids and cholesterol, enabling micelle utilization. It forms proteolysis-resistant dimers when present in the duodenal lumen. Activated phospholipase hydrolyses phospholipids to FFA and lysophospholipids. It is the only non-proteolytic enzyme stored as an inactive precursor before secretion.

Regulation of pancreatic exocrine secretion

Pancreatic exocrine secretion is mainly under autonomic nervous control in the cephalic phase of ingestion and hormonal and enteropancreatic reflex control during the gastric and intestinal.[10] In this phase, mainly enzymes are secreted but a vasodilatory response is initiated through kallikrein secretion catalysing the production of vasodilatory bradykinin, increasing the pancreatic blood flow and consequently fluid secretion. Ach from secondary nerve endings stimulates muscarinic receptors causing a release of Ca^{2+} from intracellular stores and zymogen granule exocytosis. Without increased electrolyte flow, large quantities of digestive enzymes remain in the pancreatic ducts until the increased flow in the intestinal phase moves them towards the *Papilla Vateri*. Only 25% of total pancreatic enzyme secretion is released during the cephalic phase. During the gastric phase, hormonal stimulants stimulate pancreatic enzyme secretion by another 5–10%, together with cholinergic neural stimulation. CCK is responsible for 70–80% of the total pancreatic enzyme secretion during a meal. It is released from EEC of I-type in the duodenal and upper jejunal mucosa, when these are stimulated by fatty and amino acids during the intestinal phase. HCl is less potent a stimulant. CCK-I receptor stimulation induces increased $[Ca^{2+}]_i$ and zymogen exocytosis. Trypsin exerts negative feedback by inhibiting CCK release.[10]

Secretin is a 27 amino acid inducer of electrolyte secretion. It has been suggested to act by augmenting inward potassium currents in acinar cells increasing Cl^- and HCO_3^--secretion. Acid released in the duodenum stimulates S-cells in the intestinal wall to release secretin stimulating alkaline fluid secretion from ductal and centroacinar cells. The $[HCO_3^-]$ can reach 150 mM. Fatty acids, less potently, contribute to the release of secretin. HCl reacts with HCO_3^- and Na^+ to form H_2CO_3 and NaCl. H_2CO_3 dissociates into H_2O and CO_2, the latter subsequently expired through respiration. CCK and Ach potentiates the secretion of alkaline fluid induced by secretin.[10]

Somatostatin inhibits secretion through suppression of CCK and secretin release. Its release, stimulated by the same hormones and gastrin, illustrates another negative feedback mechanism. The identification of somatostatin receptors on acinar cells suggests an independent action.[10,11]

Hepatobiliary secretions

Bile aid fat digestion through emulsification and micelle formation, and carries metabolic waste products and toxins from the blood. The efficacy of the former task is increased through the meal synchronized-contraction of the gall bladder and entry of this concentrated bile into the duodenum. The concentrating effect is achieved through the osmotic absorption of water through electrically 'leaky' tight junctions driven by active absorption of sodium over the apical and basolateral membrane of the epithelial cell to the blood, and through aquaporin channels.

Bile secretions are divided in two groups: hepatocyte secretion consisting of bile salts as the major component, along with cholesterol, lecithin, bilirubin, fatty acids, excreted conjugated metabolites, albumin, immunoglobulin A (IgA), and plasma electrolytes, and cholangiocyte secretion containing alkaline saline. The liver parenchyma shows functional hexagone shaped microscopic units in which hepatocytes modify contents of arterial and portal blood (Figure 3).

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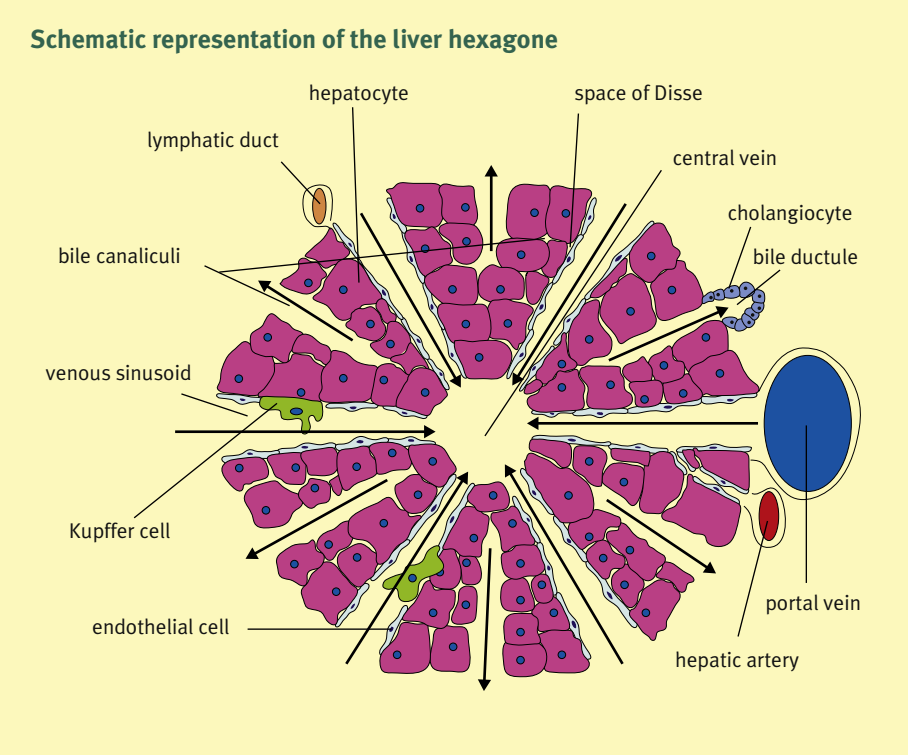

Figure 3 The liver parenchyma is organized in hexagones where hepatocytes modify contents of arterial and portal blood. In each corner is a hepatic triad consisting of distal portal vein, hepatic artery, and proximal bile ductule. The arrows indicate the direction of flow. This counter-current system allows for hepatocytes to absorb substances for modification from the blood and excrete metabolites along with bile constituents into the bile ductule. Excess fluid in the space of Disse beneath endothelial cells drains into the lymphatic ducts.

Bile acids are derived from cholesterol, and combine with sodium or other monovalent cations. The main bile acids are cholic and chenodeoxycholic acids which combine with taurine or glycine before sodium. Bile salts emulsify fat, increasing the fat water-interface and enzymatic fat digestion.

Bile salts are taken up from the enterohepatic circulation via hepatocyte basolateral sodium co-transporters. A concentration gradient is created by Na^+/K^+-ATPase Na^+-extrusion. Apical secretion into the canaliculi occurs through an active transport. As they enter the canaliculi they are stored in micelles.

Lecithin is the major phospholipid secreted with bile. It is mainly derived from the hepatocyte cell membrane. Cholesterol is to a major extent derived from a circulating pool, but a liver *de novo* synthesis provides a fraction.

Bilirubin is derived from erythrocyte haemoglobin and muscle myoglobin in the reticuloendothelial system (RES). The intermediate metabolite biliverdin, which is reduced to bilirubin, is also present in hepatic secretion. Gall bladder stored bilirubin tends to reoxidize generating the bile's characteristic green colour. To increase bilirubin's water solubility, bilirubin hepatocyte conjugation is mainly to glucoronic acid, whereas a minority is conjugated to sulphate. It is actively secreted into the canaliculi. Bilirubin is partly excreted with faeces. Intestinal bacteria convert unconjugated bilirubin to stercobilinogen which is more readily absorbed to the blood stream and excreted via the liver. Exposure of stercobilinogen to air reoxidizes it to stercobilin, giving faeces its dark colour. Urinary secretion of bilirubin occurs in the form of urobilinogen which is oxidized to urobilin. A minority of conjugated bilirubin will also be deconjugated by bacteria and pass back into the enterohepatic circulation.

Along with hepatocyte bile secretion, cholangiocytes secrete an alkaline saline into the ducts neutralizing the duodenal pH, optimizing conditions for pancreatic digestive enzymes as well as aiding micelle formation. This adds as much as 100% to the initial hepatocyte derived secretory volume. With increased flow, the time of contact for the hepatobiliary secretion decreases and the pH of the bile rises due to a reduced chloride/bicarbonate exchange. In post-hepatic jaundice an obstruction of the bile duct prevents entry of gall into the duodenum. As a result fat emulsification and absorption will be impeded, along with a loss of stercobilinogen causing steatorrhoea of pale colour. In the classic case the patient will also display darkened urine, and jaundice due to increased systemic levels of conjugated bilirubin.

Fat emulsification

For efficient digestion it is crucial to achieve fat emulsification. Lecithin is a major component in the micelle and also acts emulsifying in its free state. Its hydrophobic acyl side-chain resides in the fat and its hydrophilic phosphorylcholine group projects towards the water face which reduces surface tension. The amphiphilic nature of conjugated bile salts also aids this process. Lipase hydrolyses triacylglycerol forming FFA and monoacylglycerides, both used in micelle formation. Micelles have a diameter of 3–6 nm and contain 20–40 bile salt molecules. Micelle bile salts have their hydrophilic side facing the periphery and the hydrophobic sterol in the centre. With lecithin

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incorporation the primary micelle expands into a secondary micelle harbouring larger quantities of hydrophobic cholesterol molecules in its core. Their negative shells causes inter-micelle repulsion, emulsifying the fat. The micelle also aids fat absorption in the small intestine by effectively keeping the concentration of relatively water insoluble fatty acids, of more than C12, at a saturation level in the aqueous phase.

FFA are absorbed through diffusion. Once in the enterocyte triglycerides are re-synthesized from fatty acids and monoglycerides. In the circulation, these lipids are transported as chylomicrons to their site of storage or utilization. Bile salts are then reabsorbed into the enterohepatic circulation from the terminal ileum by a secondary active transport system. Fatty acids of less than C12 in length are sufficiently water soluble and do not necessarily need this system for absorption.

Regulation of hepatobiliary secretion

Gall bladder emptying requires the contraction of the bladder to be synchronized with sphincter of Oddi relaxation. Ach from vagal secondary neurons acts on the biliary tree interprandially and during the cephalic and gastric phases of digestion causing contractile pulses in the gall bladder, a slight secretion of alkaline fluid from cholangiocytes, and antegrade peristalsis of the *sphincter of Oddi*, reducing the risk of gall stone formation. During the gastric phase, vagal action is supported by gastrin from ventricle G-cells. CCK, the most potent inducer of gall bladder contraction, is released from EEC of the duodenum in response to luminal fatty acids. It acts on CCK-I receptors on gall bladder smooth muscle cells but also facilitates release of Ach from gall bladder ganglia initiating contraction through a rise in $[Ca^{2+}]_i$. The same hormone inhibits the contractions of the sphincter Oddi which ensures release of bile into the duodenum. Sympathetic neurotransmitters such as adrenaline and NA relaxes the gall bladder.[12] Bile acids inhibit further CCK release from the duodenum.

Secretin is the major stimulant of cholangiocyte alkaline secretion. It is released from S-cells in the duodenum and induces an increase in cholangiocyte $[cAMP]_i$, activation of PKA and opening of the CFTR and Cl^-/HCO_3^- exchanger increasing HCO_3^- secretion. Ach potentiates the secretin effect by eliciting cAMP activity. Its sole effect appears limited. Somatostatin has an inhibitory effect on cholangiocyte secretion by interaction with the somatostatin receptor 2 ($SSTR_2$) preventing secretin-induced increase in cyclic adenosine monophosphate (cAMP) activity.[13]

Colonic secretion

Some acidic material is formed throughout the gut by bacterial metabolism, and also by the activity of a colonic H^+/K^+-ATPase. Due to HCO_3^- secretions the mucus still has an alkaline pH. The HCO_3^- secreting epithelial cells of the colon occur sparsely compared to the proximal gut, but also utilizes the CFTR and HCO_3^-/Cl^- exchanger. As water is absorbed throughout the gut, the chyme becomes progressively more viscous causing a higher mechanical stress on the intestinal walls. Goblet cells in the colon secrete mucins to produce a lubricating viscoelastic gel. The mucus also serves the purpose of protecting the intestinal epithelium from adhesion of harmful bacteria, and toxins.

The colonic epithelium regulates bodily K^+-levels, providing an accessory excretion pathway to the kidney. This occurs down a concentration gradient through the passive conductance potassium BK channel after its active absorption across the basolateral membrane by the Na^+/K^+ pump and $Na^+/K^+/2Cl^-$ co-transporter. In the distal colon K^+ is absorbed by H^+/K^+-ATPase, similar to that seen in the parietal cell. A paracellular K^+ transport has also been suggested, driven by the electric gradient.[14] Electrolyte balances is a consideration in colonic irrigation where external osmotically active volumes may initiate colonic movements and increased potassium secretion. This is of particular importance in patients where multiple pharmacologic agents, along with age, may already reduce kidney homeostatic capacity, causing an increased dependence on the colon.

Regulation of colonic secretion

The main stimulus for mucus secretion in the colon is tactile stimulation of goblet cells. Reflexes also occur via the pelvic nerves involved in defecation, co-eliciting an increase in peristalsis. Sympathetic nervous stimulation decreases colonic peristalsis and secretion.

In kidney failure, an upregulation of colonic K^+ secretion describes the regulatory function of the organ to maintain a stable serum $[K^+]$. Net colonic K^+ secretion is variable and responds to increased dietary intake by increasing secretion via increased plasma aldosterone. BK-KO mice fail to reduce plasma levels of K^+ on aldosterone administration, suggesting a regulatory role of this channel. Colonic K^+ secretion through the BK channel increases on adrenalin and PGE_2 stimulation via increased cAMP levels. Aldosterone is also an inhibitor of the H^+/K^+-ATPase, adding to the net K^+ efflux effect. Somatostatin inhibits K^+ secretion through a decrease in $[cAMP]_i$.[14] ◆

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