# MOLECULAR PHYSIOLOGY

## Digestive system

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**Keywords**

Gastrointestinal tract; Peristalsis; Small intestine; Large intestine; Gastrointestinal ormones; Gastrin; Secretin; Colecystokinin; Pancreozymin.

**Introduction**

The gastro-intestinal tract is involved in the digestion and absorption of dietary food so that it can be assimilated and used by the body. The gastro-intestinal tract consists of mouth, pharynx, duodenum, stomach, small intestine, large intestine, and rectum. They are assisted by salivary glands, pancreas and liver in the process of digestion and absorption.

Digestion is the process by which large and complex dietary molecules are converted to small absorbable forms. This process takes place in the gastro-intestinal tract. Grossly, Carbohydrates are hydrolysed to monosaccharides, proteins to the constituent aminoacids and lipids to glycerol, fatty acids, acylglycerol and cholesterol. These smaller units can now be absorbed easily.

The absorbable units, which are the products of digestion can now cross the intestinal mucosa and enter the lymph or blood and become usable by the body. This process of absorption can be simple diffusion or complex process aided by carriers and receptors.

The digestion and absorption that takes place in the gastro-intestinal tract depends on a variety of processes:

1. Mechanisms which soften the food
2. Process, which propels the food forward.
3. Role of intrinsic properties of the intestinal smooth muscle and neuronal reflexes.
4. Paracrine effects of intestinal chemical messengers.
5. Digestive enzymes secreted by the salivary glands that aid in digestion in the mouth.
6. Hydrochloric acid (HCL) formation in the stomach. Digestion in the stomach
7. Digestive enzymes secreted by the pancreas that aid in digestion in small intestine.
8. Role of gall bladder and secretion of bile from the liver
9. Absorption of the end products of carbohydrate, lipid and protein digestion : Role of gamma-glutamyl cycle in amino acid absorption.
10. Gastro-intestinal hormones.

**Structure of gastrointestinal tract**

Basically the gastro-intestinal tract consists of mouth, pharynx, oesophagus, stomach, small intestine, large intestine, and rectum. The accessory organs of digestion include salivary glands, pancreas and liver.

The digestive tract begins at the mouth into which the salivary glands pour their secretions. The mouth connects to the oesophagus via the pharynx. The oesophagus is a fibro-muscular tube about 26 cm long, which by peristalsis (expansion and contraction forward movements) propels the food into the stomach. The stomach is divided into fundus, body and pyloric part. The food mixed with stomach constituents then goes into the small intestine. The small intestine consists of the duodenum, jejunum and ileum in a sequential manner. The small intestine is about 6-7 m long. The C shaped duodenum is tubular (about 25 cm long) and receives the ducts from the pancreas and the gall bladder. The duodenum continues into the jejunum and ileum, which lie coiled in the abdominal cavity to accommodate their 6-6.5 m length. The ileum continues into the thicker and shorter large intestine, which consists of caecum, ascending colon, right hepatic flexure, transverse colon, left splenic flexure and descending colon. The large intestine is much shorter than the small intestine and is about 1.8-2.0 m long. The descending colon travels down the left side of the abdomen to end in the

12-15 cm long rectum, which ends at the anus. The anal sphincter is the termination of the gastro-intestinal tract.

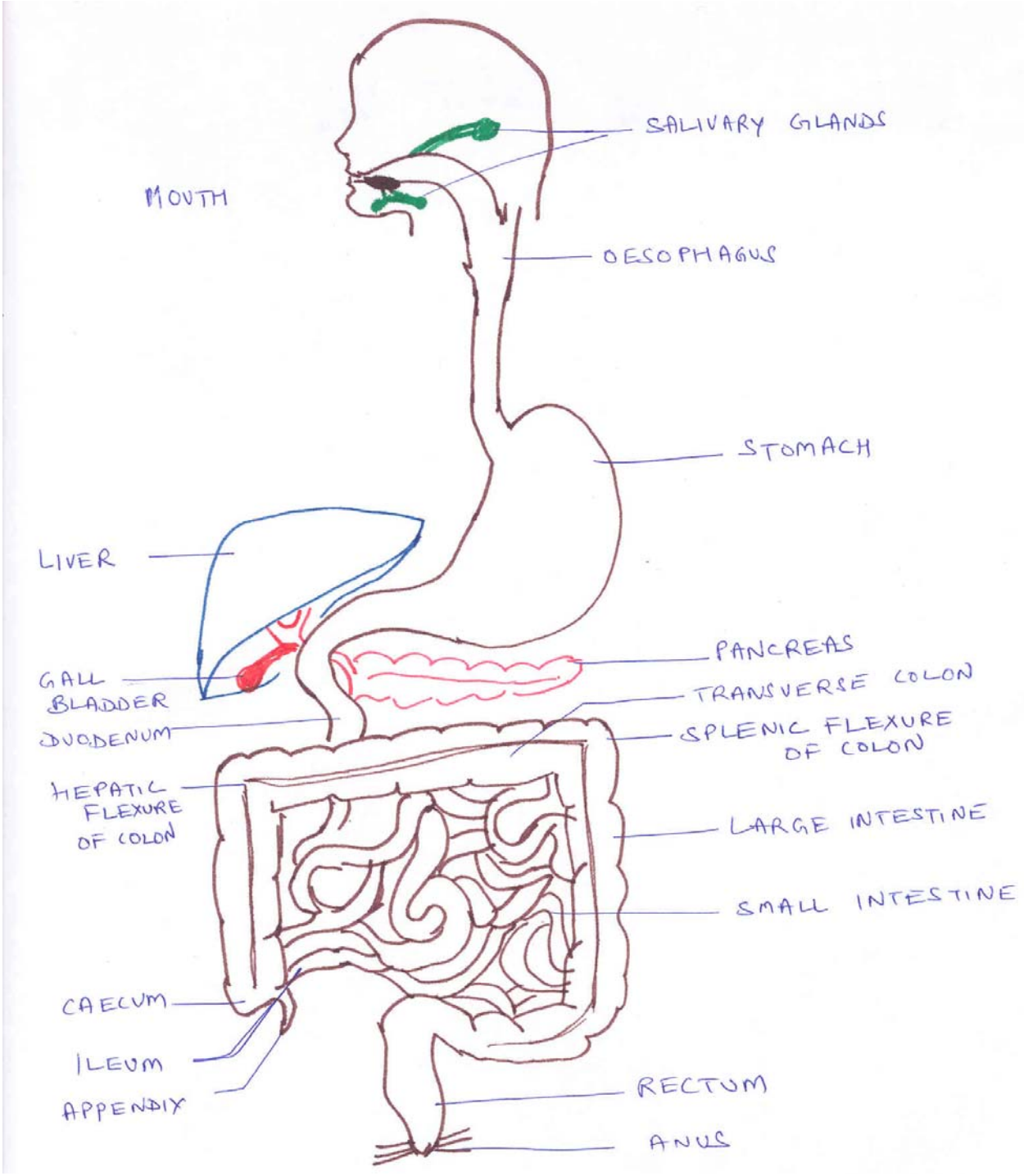


**Fig. 1: Parts of the digestive system**

Each part of the Gastro-intestinal tract essentially consists of the following structures with some local variations:

1. **Mucosa** is the innermost lining of the intestinal tract towards the intestinal lumen. It is a epithelial lining consisting of glands with a rich supply of blood vessels.

2. **Sub-mucosa** consisting of
    a. Muscularis mucosae
    b. Submucosal Meissner's plexus

   The muscularis muscle is usually longitudinal. The submucosal Meissner's plexus is involved in the control of glandular secretions.
3. **Muscularis** consisting of
    a. Circular muscle
    b. Myenteric Auerbach's plexus
    c. Longitudinal Muscle

   The longitudinal and circular muscles both help in peristalsis. They contract and expand in a required manner to propel the food forward. The Myenteric Auerbach's plexus innervates these muscles and is involved with motor control.
4. **Serosa**

   Serosa covers the gastro-intestinal tract in all places except at the oesophagus and the rectum. The nerves, lymphatics and blood vessels are supplied through the mesentry, which continues as the serosa.

***Intrinsic innervation***

The submucosal Meissner's plexus (between the muscularis mucosae and the circular muscle) and the myenteric Auerbach's plexus (between the circular muscle and the longitudinal muscle) consitute the **enteric nervous system**. These plexuses are connected by sympathetic and pare-sympathetic fibres to the Central Nervous System but can function autonomously also.

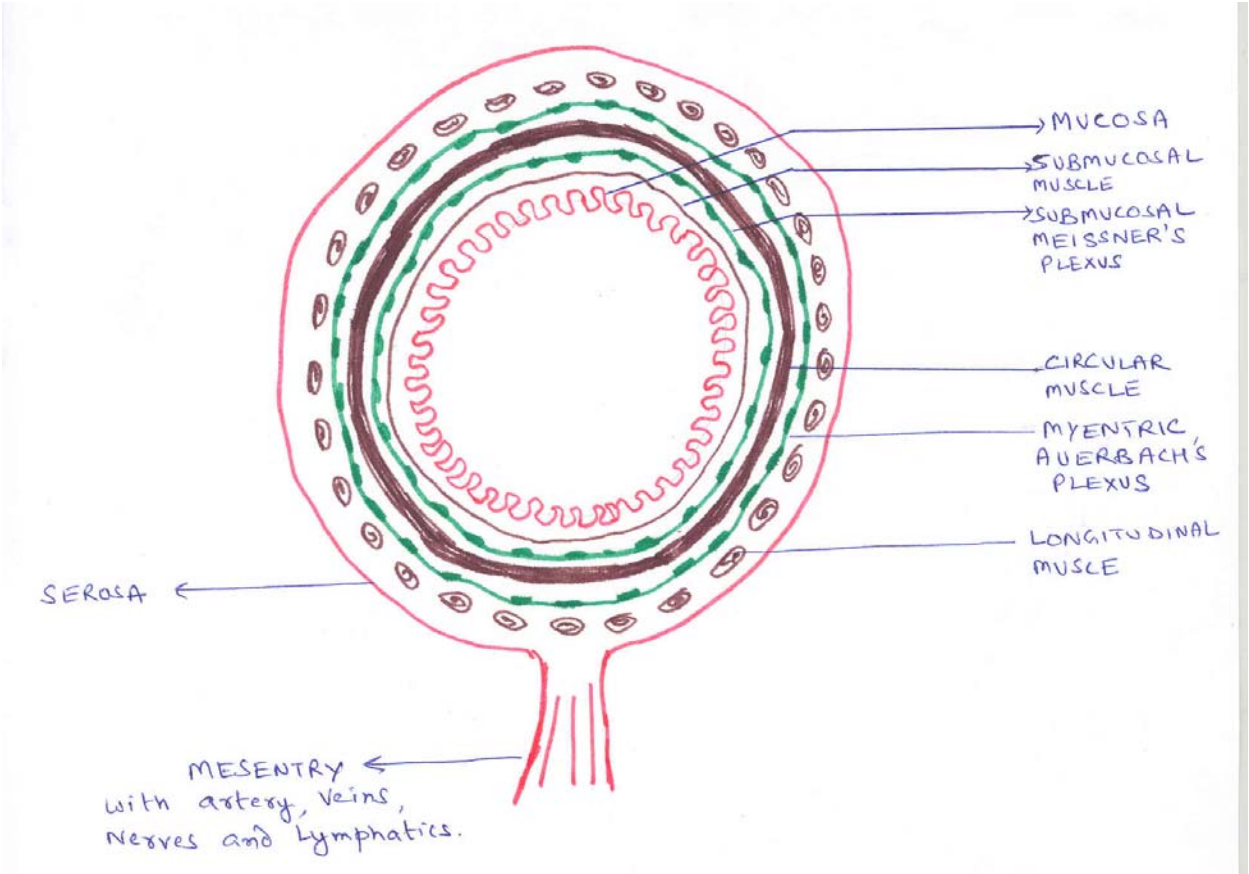


**Figure 2: Layers of wall of intestine and stomach – A generalized cross-sectional view**

The myenteric Auerbach's plexus, which innervates the circular muscle and the longitudinal muscle, is involved with motor control wheras the submucosal Meissner's plexus in the intestinal epithelium is involved with the control of intestinal secretions, glandular cells and blood vessels. The neuro-transmitters in this system include acetylcholine, norepinephrine and gamma amino butyric acid.

***Extrinsic innervation***

The gastro-intestinal tract receives extrinsic innervation from autonomic nervous system. Para-sympathetic (cholinergic) nerves release acetylcholine, cause depolarization of smooth muscle membranes and produce contraction of GIT musculature. The parasympathetic stimulation also causes relaxation of sphincters and increased secretions from stomach.

The sympathetic (adrenergic) nerves release epinephrine at their endings, which cause relaxation of GIT musculature by hyperpolarization of smooth muscle membranes. There is decrease motility, tone and contraction of sphincters.

**Peristalsis**

When the gut wall is stretched by the contents of the lumen, a reflex response is initiated such that there is a circular contraction behind the stimulus and relaxation in the area caudal to it. This is called peristalsis and is responsible for propelling the food from oral to caudal direction. The speed of this peristalsis may vary from 2 to 25 cm per second.

Peristalsis activity occurs because of the enteric nervous system. The local stretch stimulates the release of serotonin, which through activation of sensory neurons activates the myenteric Auerbach's plexus, which innervates the circular muscle and the longitudinal muscle, which is involved with motor control. Cholinergic nerves passing through this plexus in a retrograde direction release acetylcholine, which causes smooth muscle contraction. Also, cholinergic neurons passing in antegrade direction activate neurons that secrete nitric oxide and vaso-active intestinal polypeptide (VIP) causing relaxation ahead of the stimulus.

Occurrence of peristaltic activity is independent of extrinsic innervation though the activity can be increased or decreased by inputs from the autonomic nervous system.

**Regulation of motility**

The smooth muscle of the gastro-intestinal tract has spontaneous rhythmic fluctuations in membrane potential between –65 and -45 mv. This is called the Basic Electrical Rhythm (BER) and is initiated by the interstitial cells of Cajal, which are found in most parts of GIT. The BER does not take place in the oesophagus and proximal portion of stomach.

The BER itself does not cause muscle contraction. It is the spike potentials super imposed on the most depolarizing portions of the BER waves that cause muscle contraction. The spikes have a depolarizing portion because of calcium influx and a repolarizing portion due to potassium efflux. Many polypeptides and neurotransmitters like acetylcholine and epinephrine affect BER and spike potentials. The BER's coordinate peristalsis and other motor activity in the gastro-intestinal tract.

Migrating motor complexes (MMC) are modified electrical and motor activity of the intestinal smooth muscle that occur from stomach to distal ileum during periods of fasting and in between meals. The MMC migrate at a rate of 5 cm/min and occur at intervals of approximately 90 minutes. Their function is probably clearing the stomach and small intestine of luminal contents in preparation for the next meal. They stop on ingestion of food; then there is a return to peristalsis, BER and spike potentials.

**Role of mouth**

The mouth is involved in ingestion, mastication (chewing), secretion of salivary glands and swallowing of food (deglutition). The mastication or chewing breaks the larger food particles into smaller ones making it easier to swallow. Deglutition is a reflex response controlled by the vagus nerve. It is divided into oral (voluntary) stage, and involuntary (pharyngeal and oesophagal) stages.There are three pairs of salivary glands:

1. Parotid salivary gland
2. Submandibular salivary gland
3. Sub-lingual salivary gland

They contain serous and mucous cells and discharge their secretions in the mouth. Saliva has ptyalin (salivary amylase), lysozymes (bactericidal), lipases, mucin and immunoglobulin (IgA). The enzymes ptyalin and lipases are involved in the digestion of carbohydrates and lipids respectively.

**Role of stomach**

The stomach is divided into the fundus, body and pyloric (antral) part. When food enters the stomach the upper portion of stomach and fundus relax and accommodate the food. This receptive relaxation is vagally mediated and stimulated by the movement of pharynx and oesophagus. Peristalsis mixes and grinds the food. This is later followed by the contraction of distal stomach (antral systole). Regurgitation is normally avoided because the contraction of pylorus lasts longer than contraction of duodenum. The gastric mucosa has three type of gastric glands:

1 Main gastric glands
2 Cardiac tubular glands
3 Pyloric or antral glands

The main gastric glands are found in mucosa of body and fundus of stomach. They contain:

1. **Chief (zymogen, peptic) cells, which secrete pepsinogen**
   Pepsinogen is converted by hydrochloric acid (HCL) to pepsin. This pepsin is responsible for the hydrolysis of peptide bonds in proteins. Stomach has a role in protein digestion because pepsin can act at the low pH in the stomach.
2. **Parietal (oxyntic) cells, which secrete HCL**
   The plasma concentrations of $Cl^-$ and $H^+$ are 100meq/l and 0.00004 meq/l. The parietal cells are secreting HCL, which has $Cl^-$ and $H^+$ concentrations of 150 meq/l each. Hence, a mechanism to maintain this enormous concentration gradient is required.

The $H^+$ $K^+$ATPase pump present in the apical surface of the parietal cells pump out hydrogen ions into the gastric lumen in exchange of potassium ions. The hydrogen ions, which are extruded into the gastric lumen come from $H_2CO_3$ which was formed from the hydration of carbon- dioxide with the help of the enzyme carbonic anhydrase. The $HCO_3^-$ formed by the

dissociation of $H_2CO_3$ is extruded by an antiport in the basal membrane of parietal cells towards the intestinal lumen. In exchange $Cl^-$ enters the cell. The $Cl^-$ is expelled from the cell towards the gastric lumen by a concentration gradient. The $Cl^-$ and $H^+$ in the intestinal lumen form hydrochloric acid.

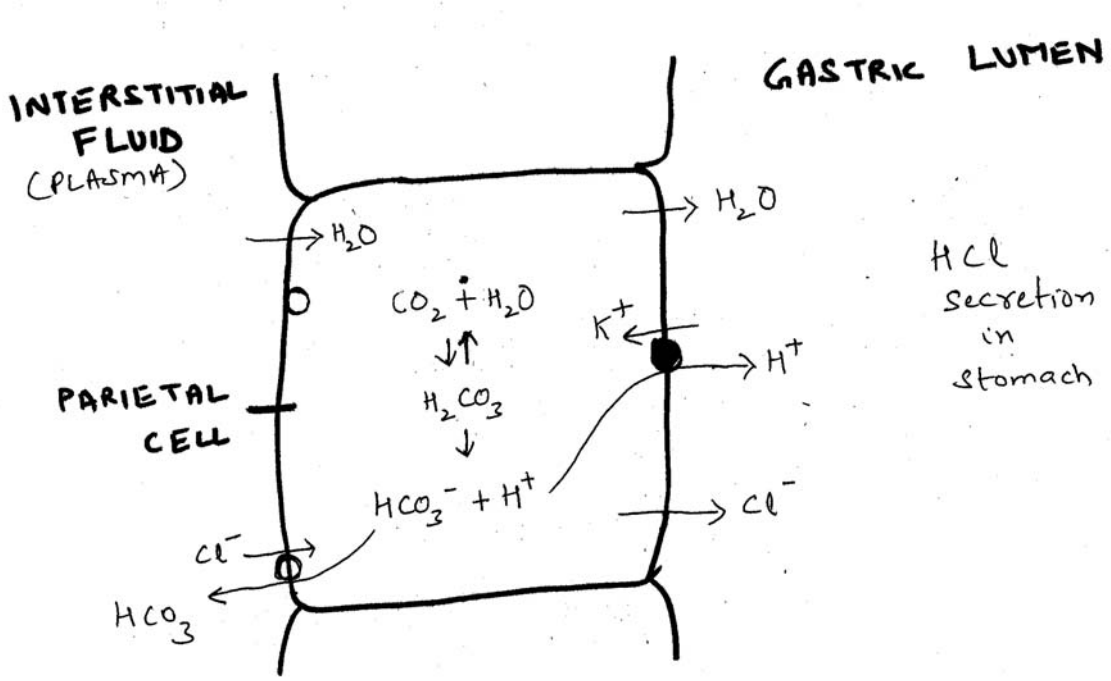


**Figure 3: HCL secretion by parietal cells in the stomach**

Regulation of acid secretion by parietal cells is by the interplay of the following factors:

1 Increase of intra-cellular calcium by acetylcholine acting on muscarinic receptors and gastrin acting on gastrin receptors.
2 Regulation of intracellular levels of cyclic AMP.

Gastrin stimulates enterochromaffin cells to produce histamine which on binding to Gs receptors increases adenylcyclase activity and therefore increased intracellular cyclic AMP.On the other hand PGE2 acts via Gi receptors to decrease production of cyclic AMP. Both cyclic AMP and Ca++ act via protein kinase to increase the transport of H+ into gastric lumen by H+ K+ATPase.

**Role of pancreas**

Pancreas is a situated near the duodenum. It has both endocrine and exocrine functions:
Exocrine function of pancreas is carried out by secretory acini and duct cells, which secrete pancreatic juice. The enzymes are stored in the form of zymogen granules, which are present in apices of acinar cells and are secreted into pancreatic ducts on requirement. The duct of Wirsung joins the common bile duct to open in duodenum. Vagal stimulation increases the secretion of pancreatic juice.

Pancreatic juice (pH 7.7-8.4) is alkaline and helps to neutralize the acidic contents of the stomach as it enters the duodenum. Besides electrolytes, pancreatic juice contains enzymes

pancreatic alpha amylase, lipase, esterase and inactive pro-enzymes trypsinogen, chymotrypsinogen and pro-carboxypeptidase A and B.

Secretion of pancreatic juice is regulated by

1. Vagal stimulation, which within minutes of taking a meal releases acetylcholine, which activates phospholipase C to cause secretion of pancreatic juice.
2. Hormonal regulation by secretin and cholecystokinin-pancreozymin (CCK-PZ).

Secretin causes release of alkaline watery pancreatic juice. CCK-PZ causes release of pancreatic juice rich in enzymes by stimulating discharge from zymogen granules. CCK-PZ also causes contraction of gall bladder. Endocrine function of pancreas is carried out by islets of Langerhans, which secrete the hormones insulin, glucagon and somatostatin.

**Role of liver**

The liver is organized into lobules, each of which has a central portal vein. Between the liver lobules are several portal spaces containing branches of bile duct, portal vein and hepatic artery.

Liver is involved in digestion, absorption, assimilation and numerous anabolic and catabolic processes. Here we will limit ourselves to the role of liver in digestion and absorption. Bile salts and bile acids are synthesized in the liver from cholesterol. They help in activation of lipase and emulsification of fats.

Bile is secreted by the cells of the liver into the bile duct, which drains into the duodenum. Between meals the duodenal orifice of the duct is closed and the bile is redirected to the gall bladder where it is stored. When food is ingested, hormones like cholecystokinin cause the gall bladder to contract and release bile into the duodenum.

Bile is made up of bile salts, bile pigments and other substances like cholesterol, fatty acids, gamma glutamyl peptidase and lecithin dissolved in an alkaline electrolyte solution. Bile acids are synthesized from cholesterol and contain the cyclopentanoperhydrophenanthrene nucleus of cholesterol. The two primary bile acids formed in the liver are cholic acid and chenodeoxycholic acid. When these bile acids reach the colon, they are converted by the intestinal bacteria to secondary bile acids, that are deoxycholic acid and lithocholic acid respectively. The bile salts are sodium and potassium derivatives of bile acids and are conjugated to glycine or taurine.

Bile salts reduce surface tension and with phospholipids and monoglycerides are responsible for micellar formation. The bile salts are amphipathic, that is, they have hydrophilic as well as hydrophobic domains. By virtue of this they can make micelles, which encompasses cholesterol and free fatty acids in the hydrophobic center. Amphipathic phospholipids and monoglycerides form the exterior of the micelle with hydrophobic tails in the center and hydrophilic heads on outside. This action of phospholipids and monoglycerides is helped by bile salts, which are similarily amphipathic in nature. So the micelle helps transport the hydrophobic fats in a polar aqueous enviroment to the brush border of the intestinal epithelial cells where they are absorbed.

Bilirubin is fomed in the body by breakdown of hemoglobin in the tissues. Bilirubin is bound to albumin in the circulation and reaches liver where it is taken up and conjugated. Free

bilirubin and bile pigments are also conjugated with uridine diposphate glucoronic acid to form water soluble bilirubin glucoronides. The glucoronides of the bile pigments are bilirubin and biliverdin and they are responsible for the yellow colour of bile.

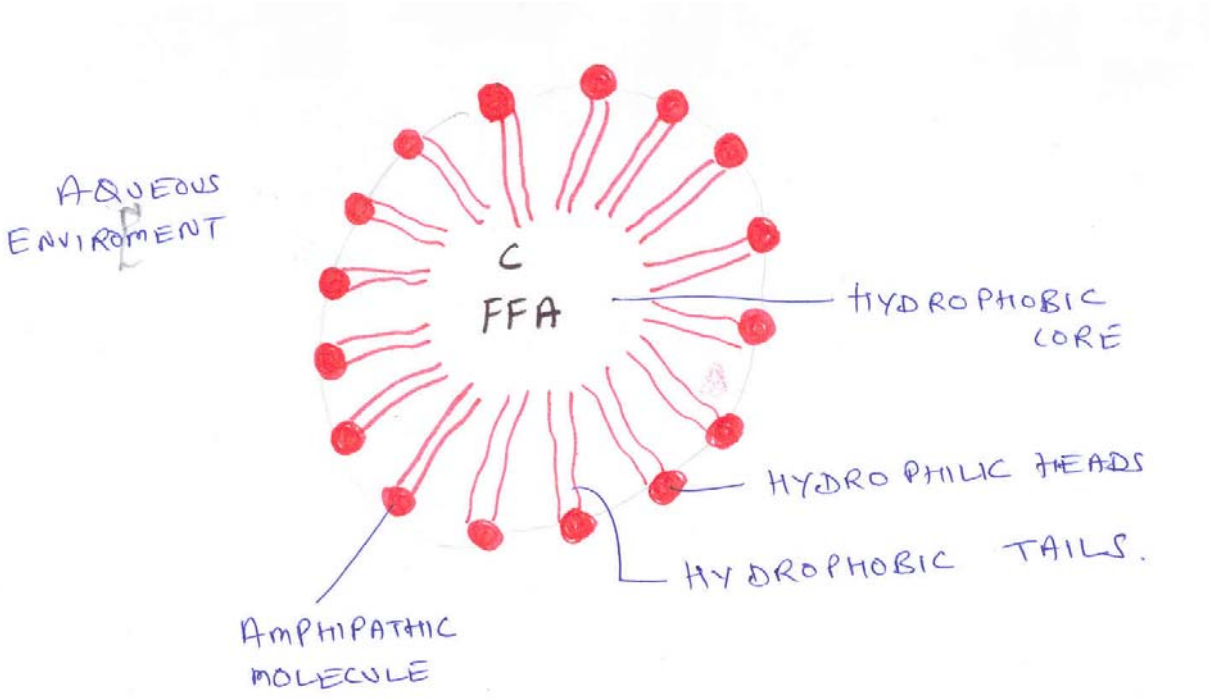


**Fig. 4: Structure of a micelle. C = Cholestrol; FFA = Free fatty acids. Amphipathic molecules include bile salts, pospolipids and monoglycerides**

**Role of small intestine**

The small intestine has the four layers as seen in other parts of the gastro-intestinal tract. The mucosal cells in the small intestine are called enterocytes. In addition to the normal structure, the entire length of the mucous membrane of the small intestine is folded into villi. Each intestinal villi is a finger like projection of mucous columnar epithelium with a network of capillaries and lymphatic vessel. There are 30-40 villi per square millimetre of mucosa. The presence of these micro-villi causes a brush border appearance of the mucosa of the small intestine. This border is rich in enzymes. It is lined on the luminal side by a layer called glycocalyx, which contains a lot of amino sugars. Solutes must diffuse across the unstirred layer and across the glycocalyx to reach the enterocyte.

The small intestine deals with about 9 litres of fluid per day (2L of dietary fluid and about 7 L from intestinal secretions). This is possible because of the micro-villi, which phenomenally increases the surface area available for absorption in the small intestine.

The food enters the small intestine mixed with secretions of the mucosal cells, pancreatic secretions and bile. The digestion of carbohydrates, lipids and proteins is completed in the small intestine.

**Role of the large intestine**

The large intestine is mainly involved with the absorption of water, sodium and minerals. It receives the digested food mixed with intestinal secretions and converts it to faeces, which is expelled through the rectum. The colon does not have villi. The fibres of the external muscular layer are organized into three bands of longitudinal muscles. The colonic glands in the mucosa secrete mucus.

**Digestion of carbohydrates**

The dietary carbohydrates, which consist of polysaccharides, disaccharides and monosaccharides are mainly digested in the mouth, duodenum and small intestine. Dietary Carbohydrates are:

1. Polysaccharides: Starch and Glycogen
2. Disaccharides: Lactose (in milk), Sucrose (in cane sugar) and maltose
3. Monosaccharides: Fructose (in fruits)

Digestion of carbohydrates occurs mainly in the mouth, duodenum and small intestine. The low pH of the stomach precludes any carbohydrate digestion at that site since ptyalin cannot act at such low pH. The various enzymes acting at on carbohydrates at various sites in the gastrointestinal tract are given in Table 1.

**Table 1: Enzymes acting on Carbohydrates at various sites in the gastrointestinal tract**

| **Source** | **Enzyme** | **Substrate** | **Products** | **Remarks** |
|---|---|---|---|---|
| Mouth | ptyalin (Salivary amylase) in saliva | starch, glycogen and dextrins | glucose, maltose and maltotriose. | hydrolyses the $\alpha$ 1$\rightarrow$4 glycosidic bonds; action stops as the food reaches the stomach as the pH in the stomach (pH = 3) is too low for the action of this enzyme. |
| Duodenum (Pancreatic juice) | pancreatic amylase ($\alpha$ amylase) | Partially digested polysaccharide | Maltose, maltotriose, oligosaccharides, $\alpha$ dextrins,limit dextrins | hydrolyses the $\alpha$ 1$\rightarrow$4 glycosidic bonds; needs $Cl^-$ for its activity.<br>Optimum pH 7- 8 is provided by pancreatic bicarbonate |
| Small intestine | Iso-maltase (endoglycosidase) | $\alpha$ limit dextrins | Oligosaccharide and maltose | hydrolyses the $\alpha$ 1$\rightarrow$6glycosidic bonds in limit dextrin |
| | Maltase | Maltose | Glucose | |
| | lactase | Lactose | Glucose,Galactose | |
| | sucrase | Sucrose | Glucose, Fructose | |

Thus the net result of carbohydrate digestion is degradation of dietary polysaccharides and disaccharides to monosaccharides, which can now be absorbed.

***Absorption of carbohydrates***

The products of digestion, mainly the monosaccharides glucose, galactose, fructose, mannose and xylose are absorbed by simple and facilitated diffusion to reach the liver through the portal venous system.Mannose and Xylose are absorbed mainly by simple diffusion. Other monosaccharides may also be absorbed by simple diffusion.

Facilitated diffusion is the preferred route for absorption of glucose, fructose and galactose. A symporter protein called translocase is present on the luminal surface of the intestinal cell membrane. It has two binding sites; one for glucose (or galactose) and other site for concurrent binding of sodium. This is named sodium glucose transporter-1 (SGLT 1). This dual binding causes the transport of both molecules to the cytosol of the enterocyte. Glucose, galactose and fructose can also enter the cell through GTUT 5 (glucose transporter 5). From the cytosol glucose or galactose leaves the cell through glucose transporter 2 (GLUT 2) and reaches blood capillaries. Sodium is transported out of the entrocyte through the sodium potassium ATPase pump.

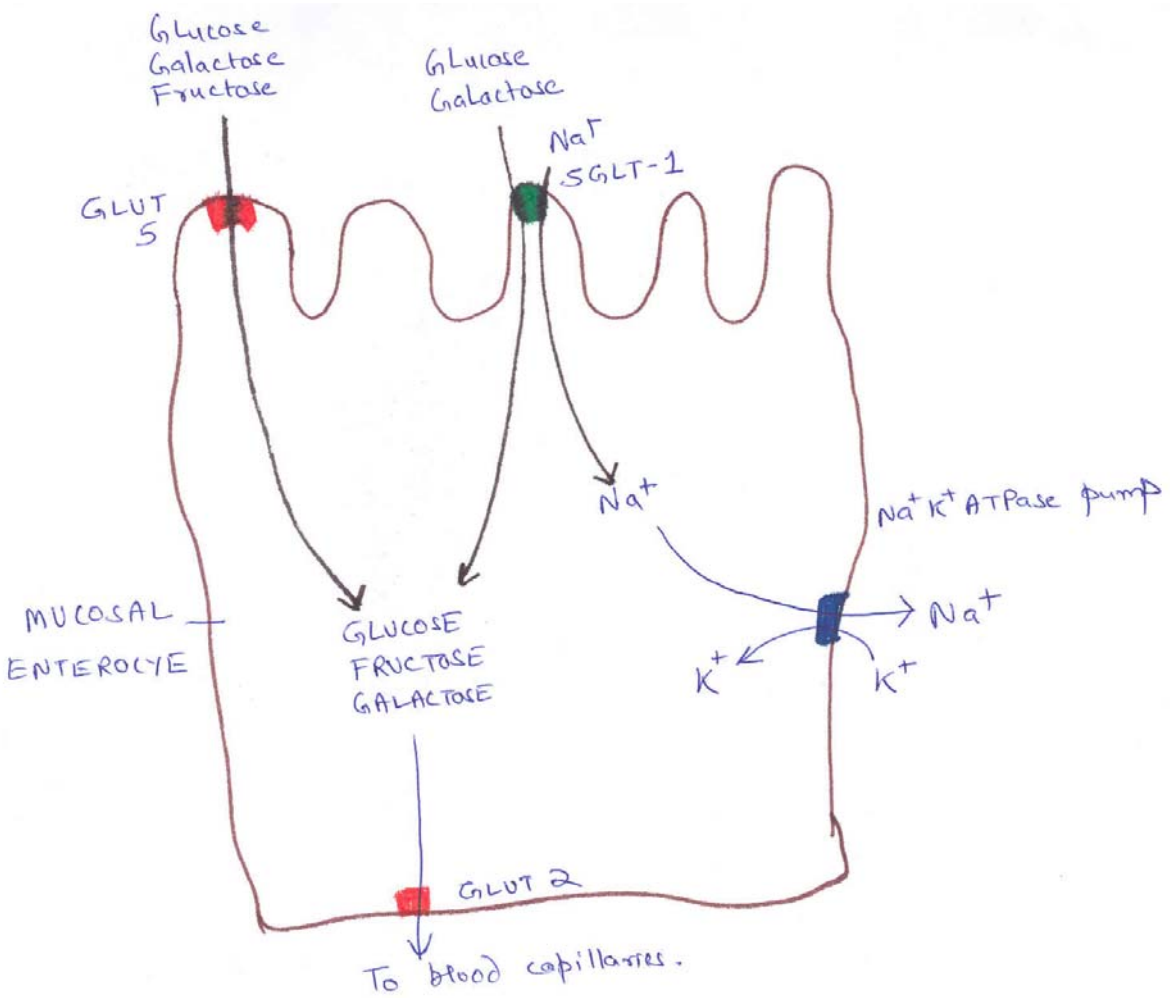


**Fig. 5: Transport of monosaccharides across enterocytes. GLUT 5 = Glucose transporter 5; SGLT 1= Sodium glucose transporter 1**

**Digestion of fat**

The dietary fat consists of long chain triacylglycerol, cholesterol esters and fat soluble vitamins (A, D, E and K). Digestion of fats begins by a lingual lipase secreted by the Ebner's gland in the tongue. This enzyme is active in the stomach also, though to a limited extent.. Though stomach also secretes a lipase, it has minimal activity. Churning activity of stomach emulsifies the fat. Pancreatic lipase secreted in the duodenum is responsible of most of the fat digestion. Fats need to be emulsified before they can be digested in the small intestine. This is done by bile salts. This emulsification by bile salts causes the formation of chyme. Furthermore, Colipase, an enzyme secreted by the pancreatic juice, helps in the attachment of pancreatic lipase to the emulsified fat. Colipase is secreted in its inactive form and is activated in the intestinal lumen by trypsin. The details of the enzymes involved in fat digestion are given in Table 2.

**Table 2: Enzymes involved in fat digestion**

| **Source** | **Enzyme** | **Substrate** | **Products** | **Remarks** |
|---|---|---|---|---|
| Lingual glands in tongue | Lingual Lipase | Triacyglycerides | Fatty acids, 1-2 diacylglycerol | |
| Pancreas | Pancreatic Lipase | Triacylglycerol | Monoglycerides and fatty acids | Requires colipase and bile salts for its activity; hyrolyses ester linkages of triglycerides |
| | Cholesterol ester hydrolase | Cholesterol ester | Cholesterol | |
| | Phospholipase A2 ( an esterase) | Phospholipids | Fatty acids, lysohospholipids | Activated by trypsin |
| | Lysopospholipase ( an esterase) | Lysophospholipids | Glycerophosphocholine Free fatty acid | |

**Mixed micelles** are formed in the intestinal lumen particularly upper jejunum. Pancreatic lipase and colipase hydrolyse triglycerides to monoglycerides and free fatty acids. Phospholipids and cholesterol esters are also hydrolysed (Table 2). The lipid mixture is now emulsified by bile acids to form mixed micelles.

***Absorpton of lipids***

The absorption of fats requires the formation of micelles. Fats are emulsified in the small intestine. The micelles move down their concentration gradient through the unstirred layer to the brush border of the mucosal cells. The lipids diffuse out of the micelle into the enterocyte and a saturated aqueous layer of the lipids is maintained in contact with the brush border of the mucosal cells. Absorption of long chain fatty acids is greatest in upper part of small intestine but short chain fatty acids are absorbed from colon.

**Formation of chylomicrons in intestinal cells**: Within the enterocyte, fatty acids, monoglycerides and diglycerides are re-esterified to form triglycerides. These and cholesterol esters are coated with phospholipids layer containing cholesterol and apo-lipoproteins. This formation of chylomicron occurs in the endoplasmic reticulum of the enterocyte. The chylomicron leaves the cells by exocytosis and enters the portal circulation via lymphatics.

## Digestion of proteins

Dietary proteins are found in animal sources like milk and dairy products, meat, fish and eggs. The vegetable sources include cereals, pulses, beans, peas and nuts. Enzymes of protein digestion are secreted as pro-enzymes (inactive precursors) and are activated in the gastro-intestinal tract. There is no protein digestion in mouth. After mastication the food reaches the stomach. The various enzymes acting at the sites in the gastrointestinal tract are given in Table 3. Besides these enzymes gastric juice also contains the proteolytic enzyme Gelatinase, which acts in the acidic medium to hydrolyse gelatin to form polypeptides. Trypsin, Chymotrypsin and elastase are endo-peptidases whereas carboxypeptidases A and B are exopeptidases.

### *Absorption of amino acids*

The dietary proteins are almost completely digested to amino acids. Some oligo-peptides and di-peptides may remain. Amino acids are absorbed from the ileum and distal jejenum. Oligo-peptides and di-peptides are absorbed from the duodenum and proximal jejenum. They are carried by the portal blood to the liver.

#### *Mechanisms of absorption of L-amino acids*

There are sodium dependent carrier systems for the transport of amino-acids into the enterocyte cells lining the intestinal lumen. The transport is energy dependent and the energy is provided by ATP.

L-amino acids and sodium ions combine with a common carrier protein present on the mucosal surface of microvillous membrane in the intestine. This complex passes to the inner or cytoplasmic surface of the same membrane. There it releases free amino acids and sodium ion. Sodium is actively carried out of the cell by the sodium ATPase pump. Carrier protein comes back to the mucosal surface and the amino acids pass through the serosal membrane through a concentration gradient. From there the amino acids are transported in the portal venous blood to the liver for different metabolic processes.

Protein absorption declines with age. Absorption of foreign proteins particularly bacterial and viral take place in the **M cells (microfold cells**), which are specialized intestinal epithelial cells. This also leads to **secretory immunity** and formation of **IgA.**

#### *Role of glutathione in aminoacid absorption and the gamma glutamyl cycle*

**Meister** proposed that glutathione participates in an active group translocation of L-amino acids (except L-Proline) into the cells of small intestine, kidney, seminal vesicles, epididymis and brain. This is a cyclic pathway in which the tri-peptide glutathione (GSH; gamma

glutamyl cysteinyl glycine) is regenerated again and hence it is called the gamma (γ) glutamyl cycle.

**Table 3: Enzymes of protein digestion**

| Source | Enzyme | Substrate | Products | Remarks |
|---|---|---|---|---|
| | Pepsin | Denatured protein | Large polypeptide derivatives | Pepsin is secreted by chief cells in stomach and acts on proteins which have been de-natured by HCL in the stomach. Optimum pH = 1.6-2.5.<br>Pepsin hydrolyses the peptide bonds in proteins where the amino groups is contributed by acidic and aromatic amino acids |
| | Rennin * | Casein | Paracasein | Optimum pH=4<br>Hydrolyses peptide bonds in which there are aromatic amino acids |
| Small intestine | Trypsin | polypeptides | oligopeptides | for activity, carbonyl group must be of basic amino acids like arginine and lysine; optimum pH 7.9 |
| | Chymo-trypsin | polypeptides | Oligopeptides, smaller peptides and amino acids | Peptide bonds of aromatic amino acids like tyrosine and phenylalanine |
| | Elastase | Polypeptides | oligopeptides | Peptide bonds in which carbonyl group is contributed by glycine, alanine and serine |
| | Carboxy peptidase A | polypeptides | Smaller peptides and amino acids | A metallo enzyme containing zinc. It is an exopeptidase which hydrolyses peptide bonds from the carboxy terminal of tyrosine, tryptophan, and phenylalanine |
| | Carboxy peptidase B | polypeptides | Smaller peptides, amino acids | Exopeptidase hydrolyzing terminal peptide bonds which are connected to basic amino acids arginine and lysine |
| | Collagen ase | collagen | peptides | |
| | Aminope ptidases (exopepti dases) | Oligopeptide s and di-peptides | aminoacids | Require $Mn^{+2}$ or $Mg^{+2}$ for activity |

*Rennin is an enzyme, which is present in an infant stomach. It coverts in case of milk to para-casein. Rennin requires calcium for its activity.

** All proteases except collagenase are secreted as pro-enzymes

The various steps in the cycle include:

1. Glutathione combines with L-amino acid outside the membrane and forms cystinyl glycine and gamma glutamyl amino acid complex that is transferred inside the membrane. The enzyme for this reaction is γ glutamyl transferase.
2. γ glutamyl amino acid in presence of γ glutamyl cyclo-transferase forms 5-oxo-proline and L-amino acid.
3. The net result is the transfer of an amino-acid across the membrane. The energy is supplied by the hydrolysis of peptide bonds of GSH.
4. Glutamate is formed from action of 5-oxo-prolinase on 5-oxo-proline.
5. Cysteine and glycine are recombined with glutamate with the help of γ glutamyl cysteine synthetase and glutathione synthetase to form glutathione.
6. This GSH is regenerated by the energy provided by 3 molecules of ATP.

***Absorption of vitamins***

The fat soluble vitamins (A, D, E, and K) are absorbed with fats. Their absorption is reduced in biliary tract obstruction. Most vitamins are absorbed in the upper small intestine.

The water-soluble vitamins –thiamin, riboflavin, niacin, pyridoxine, pantothenate, biotin and ascorbic acid – are absorbed in the small intestine by carriers that are sodium co-transporters. Absorption of Vitamin B 12 and folate is sodium independent. The water-soluble vitamin B 12 is absorbed in the ileum. This vitamin binds to intrinsic factor before the complex is transported across the ileal mucosa.

***Absorption of calcium***

Calcium is absorbed from the intestine with the help of the steroid hormone vitamin D (1, 25 di-hydroxy cholecalciferol. When the levels of ionized calcium in blood is high, the levels of 1, 25 di-hydroxy cholecalciferol levels fall and vice-versa. Calcium absorption is also decreased by substances, which form insoluble salts with calcium like phytates and oxalates.

***Absorption of iron***

Most of the iron in the diet is in the ferric form whereas it is the ferrous form which is absorbed.. The gastric secretions dissolve the iron and it is reduced by ascorbic acid and other reducing substances in the stomach. Also, the iron transporters in the brush border of the enterocytes have ferric reductase activity associated with them. Almost all iron absorption occurs in duodenum. Intestinal absorption of iron is regulated by state of iron stores in the body and state of erythropoietin in the bone marrow.

***Absorption of water and electrolytes***

The gastro-intestinal tract absorbs as well as secretes electrolytes and water throughout the intestine. There are two routes of transport. One is the paracellular route and the other is the transcellular route. In the paracellular route the flow is through the tight junctions between cells because of osmotic, hydrostatic or electrical gradients. In the transcellular route the water and electrolytes cross apical and baso-lateral membranes by energy requiring specific active transport carriers.

**Gastro-intestinal hormones**

The gastro-intestinal hormones are basically active polypeptides secreted by the nerve cells and gland cells of mucosa. They act in a paracrine fashion but large amounts of these hormones can also enter the systemic circulation. These hormone-secreting cells are called **entero-endocrine cells**. Those that secrete serotonia also are called **entero-chromaffin cells**. **APUD** (amine precursor uptake and de-carboxylase) or **neuro-endocrine** cells are those, which synthesise amines in addition to polypeptides.

The GIT hormones can be classified into:

**Gastrin family**

1) Gastrin
2) Cholecystokinin – pancreozymin

**Secretin family**

1) Secretin
2) Gastric inhibitory polypeptide (GIP)
3) Vasoactive intestinal polypeptide ( VIP)
4) Glucagon
5) Glicentin ( GLI)

**Other GIT hormones**

1) Motilin
2) Gastrin releasing peptide
3) Somatostatin
4) Neurotensin
5) Substance P

***Gastrin***

Gastrin is secreted by the flask shaped G cells or Gastrin cells of the antral (pyloric) portion of the stomach mucosa. Gastrin is secreted as pro-gastrin and gets is converted to gastrin by HCL in stomach. G cells are APUD cells that is, cells responsible for amine precursor uptake and decarboxylation. Therfore they may be neural in origin.

Gastrin is also found in pituitary gland, hypothalamus, medulla oblongata, vagus and sciatic nerves. It occurs in three forms ; G 34, G17, and G 14. They differ in the number of amino acids in the polypeptide chain and derivitization like sulphation of tyrosine and amidation of carboxy-terminal phenylalanine.

G17 is the principal form of the gastric acid secretion and has a half-life of 2-3 minutes in circulation. It is inactivated mainly by the kidney and small intestine.

*Actions of Gastrin*

1. The main role of gastrin is to increase gastric acid and pepsin secretion in the stomach. The levels of gastrin are particularly high after a protein rich meal.
2. It also stimulates the secretion of histamine from the enterochromaffin like cells present in the stomach.
3. Gastrin stimulates the growth of mucosa of stomach, small and large intestine.
4. Gastrin stimulates gastric motility.

5. Gastrin causes contraction of the lower oesophageal sphincter and also causes the gall bladder to contract.
6. Gastrin stimulates release of insulin after a protein rich meal

*Factors that affect gastrin secretion ar:*

1) Luminal factors
   - Proteins and amino-acids in the stomach
   - Distension of the stomach
2) Neural factors
   - Stimulation of Vagal nerve
3) Blood borne factors
   - Epinephrine
   - Levels of Calcium

*Factors that inhibit secretion of Gastrin:*

1. Luminal factors
   - High level of hydrochloric acid
   - Somatostatin
2. Blood borne factors
   - Secretin
   - Glucagon
   - Calcitonin
   - Gastric inhibitory polypeptide (GIP)
   - Vasoactive intestinal polypeptide (VIP)

***Cholecystokinin – Pancreozymin***

This hormone derives its dual name from the fact that it was considered to be two separate hormones. Now, it is established that the hormone, which causes contraction of the gall bladder (previously named cholecystokinin) and the hormone, which causes secretion of pancreatic juice rich in enzymes (previously named pancreozymin) is one and the same. This hormone is now called cholecystokinin-pancreozymin (CCK-PZ) or commonly CCK. CCK is secreted in pre-pro –CCK form by the **I-cells** in the upper part of intestine. It is also found in neurons of cerebral cortex and in nerves of distal ileum and colon. The various forms of CCK include CCK- 58, CCK -39, CCK -12, CCK –8, and CCK- 4. The main forms found in the intestine are CCK -12, CCK –8. The secretion of CCK is increased by the presence of products of protein digestion and by the presence of fatty acids having more than 10 carbon atoms.

The main functions of CCK are:

1. Contraction of the gall bladder.
2. Secretion of pancreatic juice rich in enzymes.
3. It inhibits gastric emptying.
4. It exerts trophic effect on pancreas.
5. It increases secretion of enterokinase.
6. It augments the action of secretin in producing alkaline pancreatic juice and increasing motility of small intestine and colon.

### *Secretin*

Secretin is secreted by the **S cells** that are located in the mucosal glands in the upper part of small intestine and mediates its action through cyclic AMP. The structures of Secretin, Gastric inhibitory polypeptide (GIP), Vasoactive intestinal polypeptide ( VIP), Glucagon and Glicentin ( GLI) are similar and that is why they are grouped in one family.

*Actions of secretin:*

1. It increases the secretion of bicarbonate by the pancreas. Hence it aids in secretion of watery and alkaline pancreatic juice.
2. It augments the action of CCK in production of pancreatic juice rich in digestive enzymes.

Like CCK, the secretion of secretin is stimulated by the presence of products of protein digestion in the intestine.

### *Gastric Inhibitory Polypeptide (GIP)*

It is also called the glucose dependent insulin tropic polypeptide. As the name implies it stimulates insulin secretion in response to glucose and fat in the duodenum. It is produced by the **K cells** in the mucosa of the duodenum and jejunum.

### *Vasoactive Intestinal Polypeptide (VIP)*

This hormone is found in the nerves of the gastro-intestinal tract. It is released from the jejenum in response to fatty meals. Besides the nerves of the GIT it is also found in blood, brain and autonomic nerves. VIP contains 28 amino acid residues and is secreted by the cells of jejenum.

Vasoactive intestinal polypeptide has the following actions:

1. increases intestinal secretion of electrolytes and water.
2. inhibition of gastrin stimulated acid secretion.
3. increases action of acetylcholine on salivary glands.
4. relaxation of intestinal smooth muscles.

### *Glucagon*

Is a linear polypeptide with 29 amino acids and is produced by the **A cells** of the pancreatic islets and upper GIT tract. Its release is stimulated by a protein rich meal, CCK and gastrin. The release of glucagon is inhibited by glucose and secretin.

### *Glicentin*

GLI (glucagon like immuno-reactivity; Glicentin) Is a hormone secreted along with glucagon by alpha cells of pancreatic islets.

***Motilin***

Is a hormone secreted by the enterochromaffin cells and **Mo cells** of the stomach, small intestine and the colon. It is a polypeptide containing 22 amino- acids and is a major regulator of gastro-intestinal motility during inter - digestive phase.

***Substance P***

Is found in endocrine cells and nerve cells in the GIT and increases the motility of the small intestine

***Gastrin Releasing Peptide (GRP)***

This is the neurotransmitter at the vagal endings that terminate in the G cells. Its release causes an increase in gastrin secretion.

**Neurotensin**

Is produced by ileal mucosal cells. Its secretion increases in response to presence of fatty acids in the intestine. It inhibits GIT motility. It also increases the flow of blood to the intestine particularly ileum.

***Somatostatin***

It is produced by the **delta cells** in the pancreatic islets and GIT mucosa. It is also called **GHIH** (growth hormone inhibiting hormone). It inhibits:

1. secretion of gastrin, secretin, motilin and pancreatic exocrine fluid.
2. gastric acid secretion and motility.
3. gall bladder contraction.
4. absorption of glucose, amino-acids and triglycerides.

**Suggested Readings**


1. Harpers Illustrated biochemistry. Murray, Granner, Mayes, Rodwell Mc.Graw Hill Publication
2. Review of Medical Physiology. William F.Ganong. Mc.Graw Hill Publication
3. Davidson's Principles and Practice of Medicine. Haslett, Chilvers et al. Churchhill Livingstone Publication.