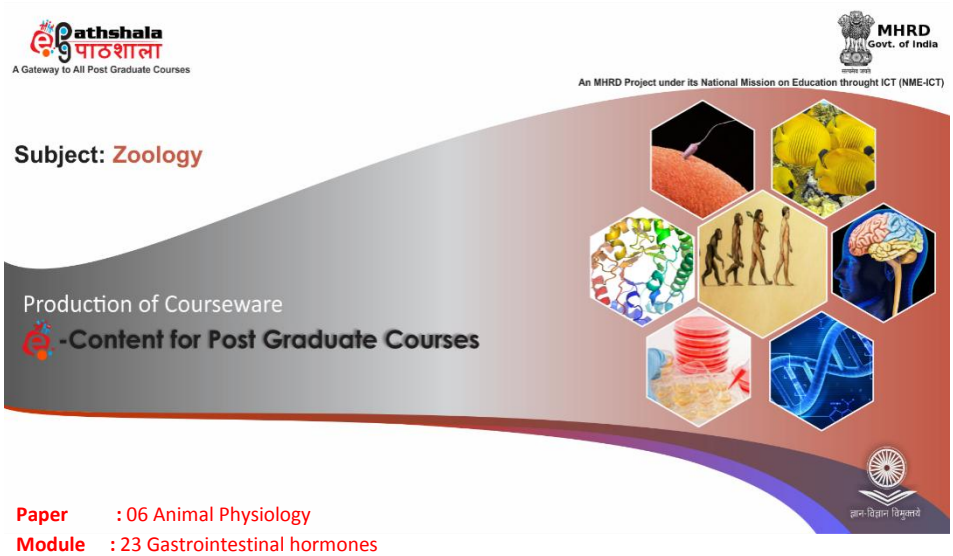

Paper : 06 Animal Physiology
Module : 23 Gastrointestinal hormones

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ZOOLOGY

Animal Physiology
Gastrointestinal Hormones

Description of Module	
Subject Name	ZOOLOGY
Paper Name	Zool 006 Animal Physiology
Module Name/Title	Neuro-endocrine Physiology
Module Id	M23 Gastrointestinal hormone
Keywords	Gastrointestinal tract (GIT), gastrointestinal hormones, GPCR, enterochromaffin cells, enteroendocrine cells, Gut-Brain Axis, receptors, Argentaffin cells, Argyrophilic cells, APUD,open cells, closed cells, ENS, myenteric (Auerbach) plexus, submucosal (Meissner) plexus, neuropeptide, neurotransmitter, Migrating Myoelectric Complex (MMC), Zollinger-Ellison syndrome,hypergastrinemia, SBS, Enterotropic actions.

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6.8. Vasoactive Intestinal Peptide (VIP)
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    1. Thyrotropin Releasing Hormone
    2. Pancreatic Polypeptide
    3. Galanin
    4. Tachykinins
7. Summary

1. Learning Outcomes

After studying this module, you shall be able to understand:

- The general anatomy of gastrointestinal tract.
- The embryonic origin of enteroendocrine cells.
- Interaction between the gut and the brain.
- The structure and synthesis of GIT hormones from enteroendocrine cells and their role to regulate GIT secretions during the process of digestion.
- Different clinical facts related to their secretions.

2. Introduction

The gastrointestinal tract is part of a majorphysiological system involved in the regulation of the body's energy homeostasis. The gastro-intestinal system is essentially a long, muscular tube running right through the body, with specialised sections including mouth, pharynx, oesophagus, stomach with 3 subparts: the fundus, the main body and the pyloric antrum, small intestine with 3 subparts: the duodenum, the jejunum and the ileum, large intestine with caecum, colon (ascending, transverse, descending and sigmoid), rectum and anus. These specialized sections can digest the food material, extracting useful components from it, and expel the residual material to outside of the body.

The entire gastrointestinal tract (GIT) has same basic structure from outside to luminal side- serosa, muscularis externa, submucosa and mucosa. The gastrointestinal mucosa is the largest endocrine organ of the body. The cylindrical (crypts), glandular and monolayer epithelial lining of the GIT mucosa undergo continuous and rapid renewal throughout the life. It has stem cells, undifferentiated crypt cells, absorptive cells, goblet cells, Paneth cells, enteroendocrine cells (EECs) (neuroendocrine cells) and M cells. The EECsare specialized epithelial cells, dispersed among mucosal cells of the gastrointestinal tract and represent less than 1% of the entire gut epithelial population. EECs are of two types- "open cells" with microvilli reached to the lumen, and "closed cells" do not extend up to the lumen. Both types of cell have their secretory products stored in secretory granules which on stimulation,

released their contents into the interstitial space by exocytosis at the basolateral membrane, where they can act locally or on distant targets through the bloodstream. In this respect, EEC "open cells"can be regarded as primary chemoreceptors, capable of responding to luminal constituents by releasing secretory products that activate neuronal pathways, nearby cells or distant targets through different mechanisms. However, luminal contentsregulate "closed" cells indirectly through neural and humoral mechanisms.

Enteroendocrine cells releasing more than 15 different polypeptide local hormones or signal molecules includinggastrin, ghrelin, somatostatin, cholecystokinin (CCK), secretin, vasoactive intestinal peptide (VIP), serotonin, glucose-dependent insulinotropic peptide (GIP), glucagon-like peptides (GLPs), motilin, peptide YY (PYY), serotonin, histamine etc and all act locally in autocrine or paracrine manner.

GIT activities are controlled by hormones releasing from the brain or by GIT itself. The presence of food in the GIT stimulates different hormones secretions which regulate digestive juice secretion, increased gut motility, enzyme release, peristalsis etc. These hormones work in association with the enteric nervous system (ENS) also, which co-ordinates with the brain to control various functions of the digestive organ such as give appetite signal to brain, satiety, energy expenditure and metabolism, stimulus for alkaline secretions, to control efficiency of digestion, controlling gastric emptying, gut motility, metabolism etc. The two important components of ENS are-**myenteric** (**Auerbach**) and the **submucosal** (**Meissner**) plexuses. The Myenteric plexus lies in between the longitudinal and circular smooth muscles and coordinates the contraction and relaxation of intestinal wall. The Meissner plexus is situated in submucosa of the intestinal wall and regulates the gut internal environment, blood flow, epithelial cell functions and secretion. Like Central Nervous System (CNS), enteric neurons release neurotransmitters such as acetylcholine, dopamine, serotonin, tachykinins, VIP, NO, GIP, NPY, GRP (Gastrin releasing Peptide), CCK and neuropeptides including Secretin, Galanin, PYY and neurotensin.

3. Embryonic origin of Enteroendocrine cells (EEC)

The origin of EEC is little controversial, as few scientists suggested its development from endodermal cells while others by neural crest. However, experimentally it demonstrated that except EECs, most of the epithelial cells in intestinal mucosa are differentiated from pluripotent stem cells at the base of crypts (or the neck region of gastric glands), hence these cells are endodermal in origin, while enteroendocrine cells are based on APUD concept. AUDP cells are a group of cells which originate by a common embryonic neural crest, are ectodermal in nature. APUD cells consisting of following characteristic activities:

Amine Precursor Uptake (APU): intake of amine precursors such as 5-hydroxytryptophan and dihydroxyphenylalanine. **Decarboxylase (D)**: enzyme amino acid decarboxylase (which convert precursor to amine). These cells share common characteristics of secreting peptide hormones including secretin, CCK, gastrin, VIP and many others. The neuroendocrine cells have been divided into two types:

1) **Argentaffin cells:** have serotonin filled granules able to reduce silver nitrate. Argentaffin cells are oval or triangular, stain positive with bi-chromate salts and are called enterochromaffin cells. These cells have pale cytoplasm filled with dark-stained granules and a basal position in relation to the remaining epithelial cell. These epithelial cells are primarily present in small intestine and appendix.
2) **Argyrophilic cells:** have granules that reduce silver nitrate only in the presence of a chemical reducer.

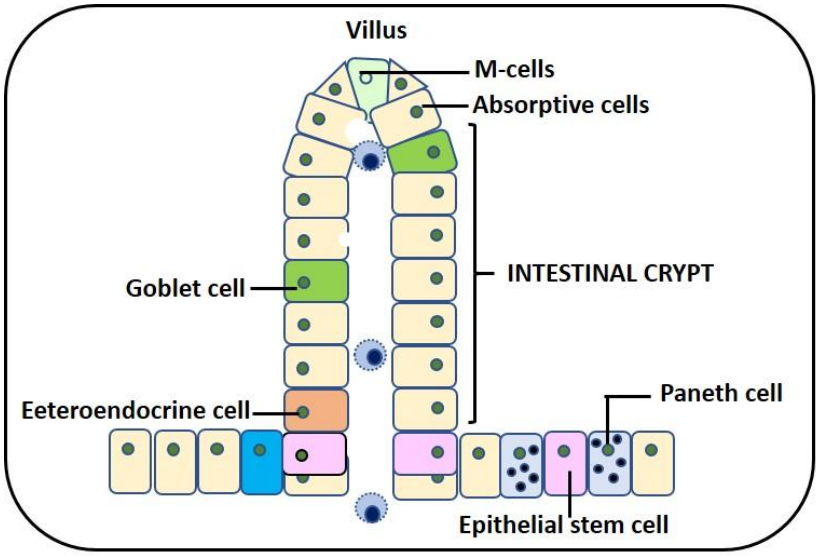

Figure 1: Location of Epithelial stem cells in intestine.

(Source: Authors)

4. Types of Enteroendocrine cells

The nerve cells and glandular cells, present in the GIT release gastrointestinal hormones into the blood stream by diffusion as local hormone or by enteric nervous system, in response of various stimulations as shown in below given table 1.

Table 1: Types of Enteroendocrine cells with their location, receptors, and other factors.

Entero-endocrine cells	Location	Releasing hormone/s	Receptor and primary signalling pathway	Distribution of the receptor	Stimulators& regulators
G	Stomach & duodenum	Gastrin & TRH	CCK-2 ↑ Gq- in Ca^{++} and PKC	Gastric ECL and parietal cells	Luminal amino acids &calcium
I	Stomach, Duodenum & jejunum	CCK	CCK-1 ↑ Gq- in Ca^{++} and PKC	Gall bladder muscularis Pancreatic acinar cells Pancreatic duct Vagal afferent and enteric neuron Gastric D cells	**Stimulator:** Saturated fat, long chain fatty acids, amino acids & Peptides **Regulator:**Trypsin

S	Duodenum & proximal jejunum	Secretin	Secretin receptor ↑ Gs- in cAMP	Pancreatic and biliary duct Pancreatic acinar cells G cells	**Stimulator:** Gastric acid, bile salts, & luminal nutrients **Regulator:** Somatostatin
L	Duodenum colon & rectum	GLP-1, GLP-2 & PYY	GLP-1 and GLP-2 receptor ↑ Gs- in cAMP	β cells of pancreatic islets GI tract-small intestine	Direct - Lipids & carbohydrates, Indirect-neurohormonal signals by GIP
PP	Endocrine pancreas	PP	Y4 and Y5	Entire GIT mucosa	
K	Duodenum & proximal jejunum	GIP	GIP receptors ↑ Gs- in cAMP	β cells of pancreatic islets gastric mucosa and muscularis	Long chain fatty acids, Triglycerides, Glucose, Amino acids
N	Small intestine-ileum	Neurotensin	NTR-1, NTR-2& NTS-3 (Sortilin)	Brain & intestine	Lipids
M	Duodenum & proximal jejunum	Motilin	Motilin receptor ↑ Gq- in Ca^{++} and PKC	Smooth muscles and enteric neuron of stomach and small intestine	**Stimulator**: By alkalinisation of small intestine **Regulator**: By the presence of food or acid
P	Fundus of the stomach	Ghrelin	GHS receptor type 1a ↑ Gq- in Ca^{++} and PKC	All parts of GIT	**Stimulator:**Secretion during **fasting** **Regulator**: when stomach is full
D	Stomach, duodenum & colon	Somatostatin	SST-1 TO SST-5	Stomach, Duodenum, pancreas,	Intestinal hormones, neurotransmitters, Carbohydrate and protein
Enteric neurons, Afferent neurons	Entire GIT	NPY	Y1, Y2. Y3, Y4, Y5 and y6	Sympathetic neurons of entire gastrointestinal mucosa	Released due to stretching by Luminal nutrients
Enterochromaffin cells (ECE)	Epithelial lining of GIT	Serotonin	5-HT-2, 5-HT-3, 5-HT-4 and 5-HT-7	Mucosal terminals of the intrinsic sensory neurons	Released due to stretching by Luminal nutrients
		Histamine	H-1 to H-5	Gastric parietal cells	

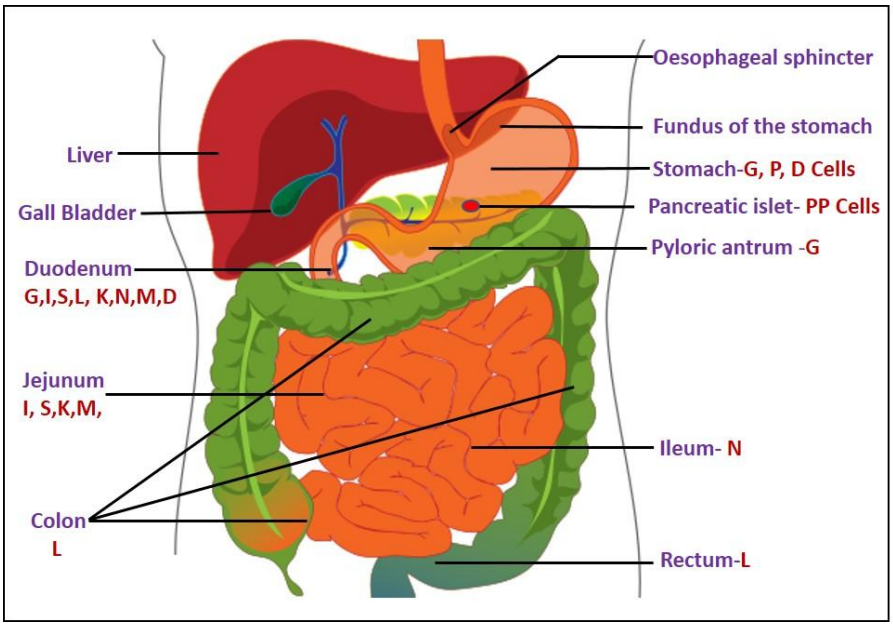

Figure 2*:* Location of different enteroendocrine cells. **(Source: Authors)**

5. Gut-Brain Axis

The gut endocrine cells secrete signalling substances and interact in an integrated manner with each other, with the enteric nervous system (ENS) and the afferent and efferent nerve fibers of the central nervous system (CNS), particularly autonomic nervous system (ANS).The hypothalamus and the brainstem are the main central nervous system regions responsible for the regulation of energy homeostasis by regulating appetite, adiposity and energy expenditure. The arcuate nucleus (ARC) of the hypothalamus is play anindispensable role in the regulation of food intake and energy homeostasis. The ARC possesses two types of neurons with opposing effects for food intake.

a) Orexigenic neurons (stimulating appetite) express neuropeptide Y (NPY) and Agouti-related protein (AgRP).

b) Anorexigenic neurons (inhibiting appetite) in the ARC express alpha-melanocyte-stimulating hormone (alpha-MSH) derived from pro-opiomelanocortin (POMC), and cocaineand amphetamine regulated transcript (CART).

The ARC has contained fenestrated capillaries near to median eminence,hence acts as an incomplete blood-brain barrier. Gut hormones are released from the gastrointestinal tract in the presence of different types of meal and give signals for short term nutrient availability to the ARC. Circulating gut hormones can pass across the median eminence and influence the activity of the ARC neurons directly. Other circulating factors such as insulin and leptin (a circulating peptide released from adipose tissue) relay information about long-term energy stores and adiposity.

Along with this, short term availability of nutrients is signalled by gastrointestinal vagal afferents. Following a meal, the vagus is activated by both mechanoreceptors and chemoreceptors. The resultant neural signals converge in the nucleus of the tractussolitarius(NTS) within the brainstem. These signals are then fed forward neuronal from the NTS to the hypothalamus. Apart from the gut nutrients, gut hormones also alter the activity of the ascending vagal pathways (gut to brainstem). Hence, numerous neural and hormonal inputs influence the hypothalamic ARC orexigenic and anorexigenic neurons.These ARC neurons in turn activate to a number of extra-hypothalamic and intra-hypothalamic regions, including particularly the hypothalamic paraventricular nucleus (PVN), where some of the important efferent pathways regulating energy expenditure arise.

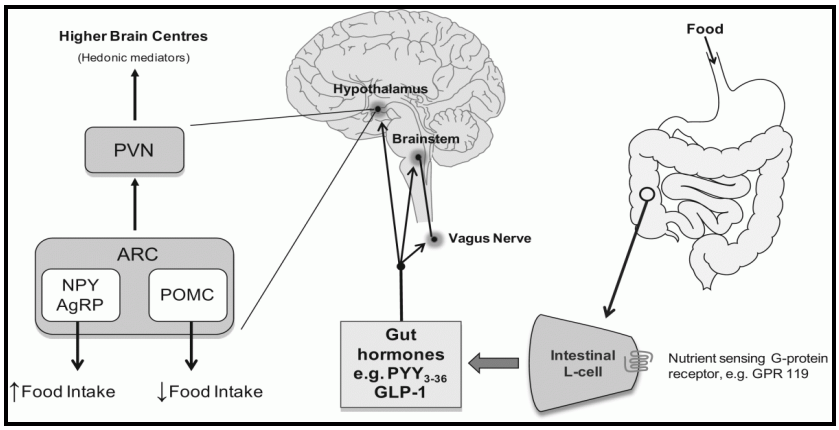

Figure 3: Gut-Brain axis-regulation of food intake. (PVN: Paraventricular nucleus)

Gut hormones such as GLP-1, Ghrelin, PYY, NPY etc. are believed to contribute to the short-term feelings of satiety and hunger. These peptides reduced food intake by decreasing hypothalamic orexigenic signalling and increasing anorectic signallingand also mediate inhibitory feedback mechanisms on intestinal transit, contributing to prolonged gastric distension, and increased satiety between meals. These combined CNS effects and 'intestinal brake' mechanisms facilitate the control of food intake and postprandial transit through the gastrointestinal tract and thereby the immediate availability of energy.

6. Gastrointestinal hormones

In our gastrointestinal tract, more than 15GI hormones are present, circulated into the blood and affect the functions of other parts of the digestive system.

6.1 Gastrin

In 1905, John Sydney Edkins postulated that the acid secretory activity of the stomach could be attributed to the hormone gastrin. Gastrin is a synthesized by "Open" type G cells where it is stored in large granules. G cells first appear in the duodenum, further, relocate in antrum and pylorusof the stomach. Activity of the G cells regulated by luminal contents as well as by humoral and neural influence. It binds to the receptors present mainly on parietal and enterochromaffin like cells.

A. Structure: The gastric gene is located on 17q21 chromosome, expressed to produce a single mRNA transcript, encodes a preprogastrin of 104 amino acids at the endoplasmic reticulum where it undergoes to post-translational change at N-terminal sequence. Hence, due to post-translational changes it cleaved in between an alanyl and a seryl residue to get 71aa long progastrin. Formed progastrin is passes to the golgi complex, then trans-Golgi networkand packed into the secretory vesicles. In secretory vesicles, dibasic C- terminal sites are cleaved by prohormone convertases to give peptide G34-Gly. (Prohormone convertases can also cleavedthe C-terminal sites of G34-Gly to give G17-Gly.) PAM (peptidylglycine Alpha-Amidating Mono-oxygenase) enzyme finally converted G34-Gly into biologically active G34 which again cleaved into mature G17 (Note: PAM enzyme does not directly

convert G17-Gly into mature G17). Both mature G34 and G17 are considered as "Classical" gastrin, stimulate gastric acid secretion whereas G34-Gly, G17-Gly and progastrin are "Non-classical" gastrin. G34 is predominant in the duodenum whereas G17 (molecular weight 2,000 kd) mainly in the gastric antral mucosa. These two are the predominant circulating forms.The functional activity of gastrin resides in the terminal four amino acids Trp-Met-Asp-Phe-NH_2.

A synthetic gastrin, composed of the terminal four amino acids of natural gastrin along with the amino acid alanine, possess same physiologic properties as the natural gastrin. This synthetic product is called **Pentagastrin**.

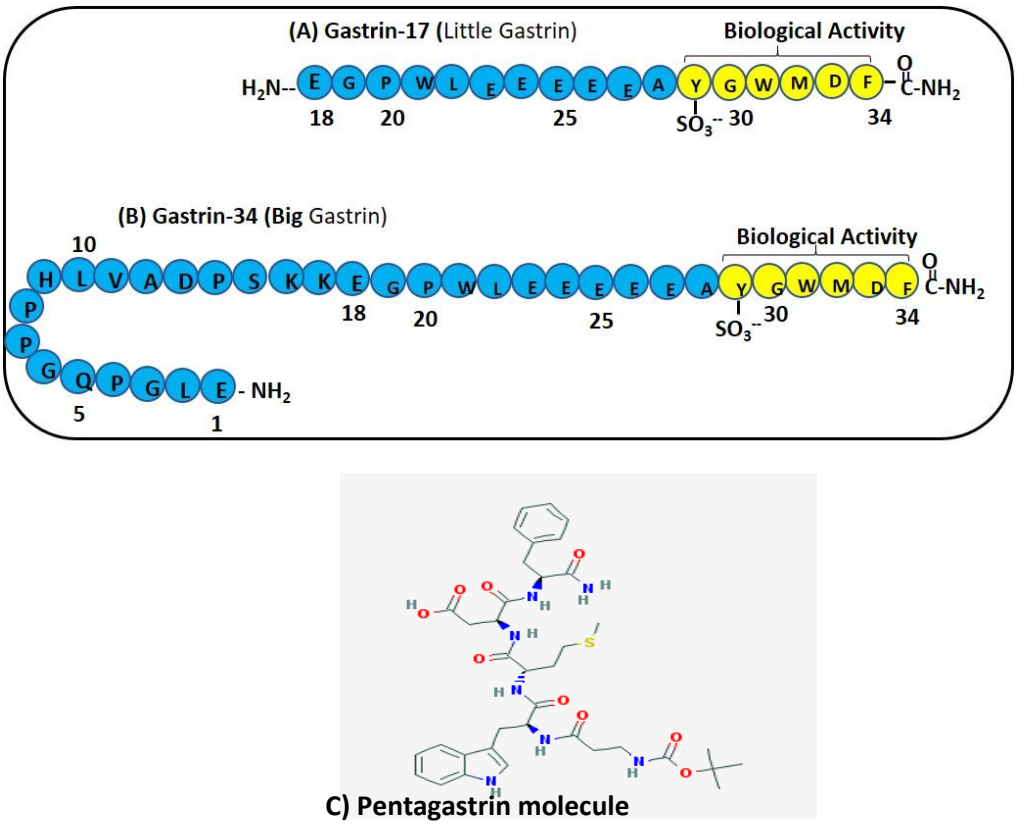

Figure 4: Types of Gastrin molecule.

B. Mode of action: Cephalic stimulation through the parasympathetic system (ACh) can release gastrin from the G-cells of gastric antrum mucosa. Mature gastrin via systemic blood circulation of the body reached to stomach and stimulates the secretion of histamine from Enterochromaffin like cells of gastric fundus which in turn via paracrine diffusion induce

acid secretion by binding with histamine-2 receptors located on the oxyntic mucosa and parietal cells.

C. Physiological functions: The initiation for the secretion of gastrin begins due to the presence of protein food stuffs and calcium. After protein ingestion and gastric distension, gastrin releases to stimulates gastric acid secretion and has a trophic effect on the gastric mucosa. Gastrin has brought following important functions on the GIT:

- **i.** Release gastric acid from stomach.
- **ii.** It also activates the synthesis of histidine decarboxylase enzyme responsible for histamine secretion.
- **iii.** Mature gastrin upregulates the K^+/H^+ ATPase pumps into the apical membrane of parietal cells which increases the H^+ ion secretion into the stomach.
- **iv.** It promotes the maintenance and proliferation of gastric epithelium and also acts as a growth factor for the gastric mucosa.
- **v.** Gastrin is attached with CCK2 receptors expressed in the pancreas to promotethe secretion of glucagon.
- **vi.** It inhibits the secretion of somatostatin from the D cells of pancreatic islets.

D. Clinical facts: Gastrin has been induced colon cancer cell lines expressing the CCK2 receptors (normal colonic epithelium does not express the CCK2-R). It is also involved in the acceleration of malignant tumour formation of gastric mucosa by inhibiting apoptotic activity and stimulates invasion and migration of epithelial cells. The presence of gastrin secreting neoplasms leads to Zollinger-Ellison syndrome in the pancreas, duodenum and in the gastric antrum which is associated with the hypergastrinemia (Excessive gastrin secretion).

6.2 Cholecystokinin

Cholecystokinin (CCK) also called pancreozymin plays very important role in digestion in the small intestine. Cholecystokinin name was given by its discoverers, Ivy and Goldberg for its gall bladder contraction activity while pancreozymin by Harper and Raper for its pancreatic secretion activity. Later, in the laboratory, based on their properties it was concluded that both are identical and combinedly named as CCK. CCK gene is located on the

chromosome 3p22-p21.3, that expressed in the enteroendocrine "Open" type I cells in the duodenum and jejunum. CCK stimulates the secretion of pancreatic digestive enzymes and bile from the gall bladder in response of amino acids and fatty acids in chyme.

A. Structure: Cholecystokinin (CCK) / pancreozymin is a polypeptide hormone, synthesised as a preprohormone with 94 amino acid, which is post-translationally processed into multiple molecular forms of CCK-83, -58, -39, -33, -22, -8 and -5 with all share a common C terminus. The CCK-33 is the dominating circulating form while CCK-8 is the biologically active form with sulphated tyrosine residues at position 7 from the COOH terminus, which is necessary for its biological activity.

It has 2 receptors CCK1-R which previously termed as CCK-A where "A" stands for Alimentary canal and CCK2-R, previously termed as CCK-B where B stands for Brain. CCK1-R is binds and gives response to sulphated CCK with 500-1,000 folds higher affinity than the sulphated gastrin molecule or non-sulphated CCK. CCK2-R binds and responds to gastrin and CCK with same potency but mainly considered as "gastrin receptor". The terminal five amino acids in the gastrin and cholecystokinin molecular chains are the same.

B. Mode of action: Once occupied, CCK receptors stimulate production of second messenger IP_3 and DAG. The IP_3 causes an increase in cytosolic Ca^{++} and DAG activates phosphokinase C.CCK evokes the release of pancreatic juice in the presence of secretin more effectively. ACH also cause extrusion of zymogen granules from the acinar cells of the exocrine cells of pancreas, indicating direct parasympathetic (Cephalic) control of enzyme release from exocrine pancreas.

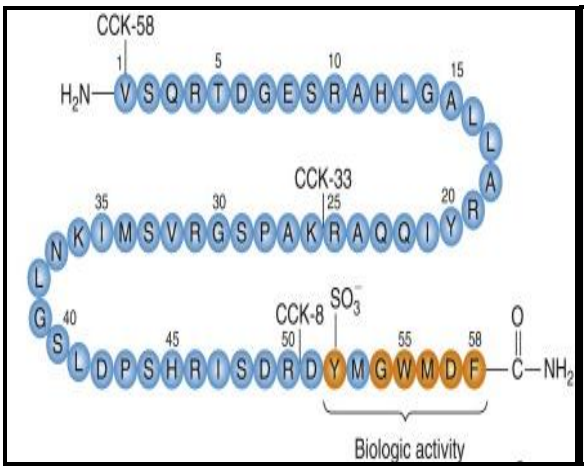

Figure 5: Structure of Cholecystokinin molecule.

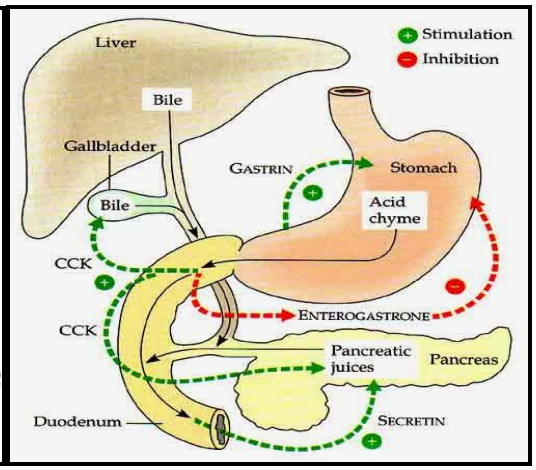

Figure 6: Mode of action of CCK, Secretin and Gastrin.

C. Physiological function: Depending upon the region of gut, the effects of CCK on GIT either by direct release from the I cell or neurons mediated or both. Neurons mediated activities either contraction or relaxation, depends upon the released neurotransmitter from the neurons under the influence of CCK.

i. It has potent effects on gut smooth muscle contractility.

ii. Acts as neurotransmitter in the nerve fibers of gastric and colonic myenteric plexus and submucosal plexus.

iii. Regulates the contraction of gallbladder via acetylcholine secretion from the neurons.

iv. It also relaxed the sphincter of Oddi mediated by inducing secretion of Vasoactive Intestinal Peptide (VIP) under the influence of CCK.

v. Inhibit gastric emptying. Under the influence of CCK, an inhibitory vago-vagal reflex generates which causes VIP-induced relaxation of the gastric fundus. All these functions regulate the flow of chyme in the duodenum.

vi. Stimulates pancreatic enzyme secretion.

vii. Assists in long-term maintenance and health of organs critical for fat and protein digestion by inducing a trophic effect on the exocrine pancreas and gallbladder.

D. Clinical facts: Diseases resulting from excessive or deficient secretion of cholecystokinin are rare. A person affected with polyglandular syndrome type I exhibited severe diarrhoea

and malabsorption in association with reduced numbers of enteroendocrine cells and CCK deficiency. Thus, CCK secretion in response to oral nutrient ingestion likely regulates nutrient absorption and postprandial satiety.

6.3 Secretin

The gastrointestinal peptide hormone, secretin, was identified by Bayliss and Starling in 1902. It was the first hormone to be discovered. Secretin is secreted by S cells of the duodenal mucosa in the crypts of Lieberkühn in response to acid in small intestine. Secretin receptors are G-protein coupled secretin receptors (SR) expressed in the basolateral membrane of several cells. Secretin is also considered as a neuropeptide hormone as it is expressed in theCNS.

A. Structure: The human secretin genepresent on chromosome 11p 15.5, is 514 bp long, with an N-terminal signal peptide, spacer, secretin itself (residues 28-54) and a 72-amino acid C-terminal peptide. This peptide is proteolytically processed to yield a single linear 27-amino acid peptide hormone (with a molecular weight of 3,400kD) by removal of the signal peptide, plus amino and carboxy-terminal extensions. All the amino acids in the secretin molecule are essential for it biological activity. The sequence of the mature peptide has homology to that of other peptides isolated from the gastrointestinal tract including GLPs, vasoactive intestinal peptide (VIP) and gastric inhibitory peptide, which are the members of the secretin family.

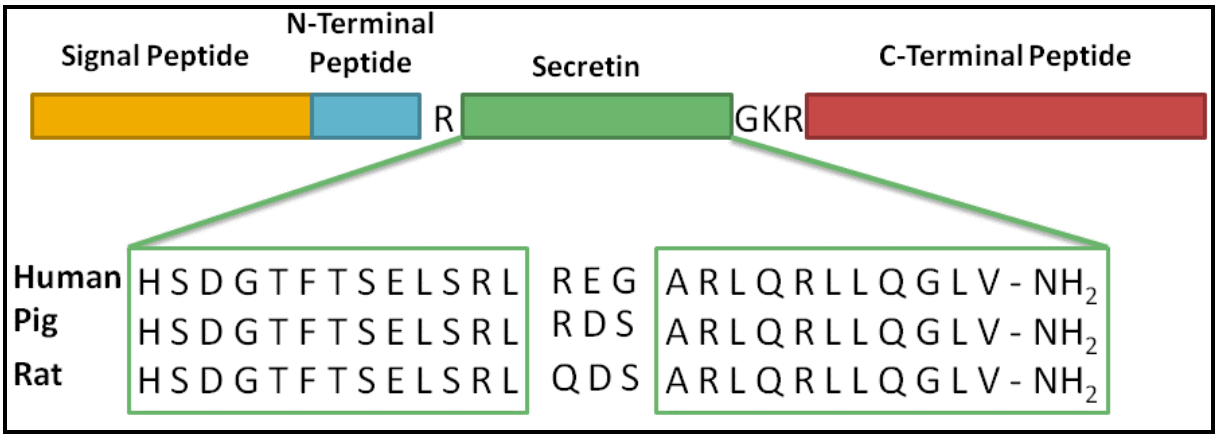

Figure 7. Structure of Secretin in different mammals.

B. Mode of action: When acid chyme with pH less than 4.5 to 5.0 enters the duodenum from the stomach, it causes duodenal mucosal release and activation of secretin, which is then absorbed into the blood. The one truly potent constituent of chyme, the hydrochloric acid causes secretin release. Secretin in turn causes the pancreas to secrete large quantities of fluid containing a high concentration of bicarbonate ion (up to 145 mEq/L) but a low concentration of chloride ion. cAMP signalling plays a key role for the secretion of bicarbonate ions from the pancreatic ducts. Secretin-induced bicarbonate secretion depends on the activation of the cAMP-dependent anion channel, CFTR (*Cystic fibrosis transmembrane* conductance regulator), which is confined in the apical membrane of various epithelia including pancreas and bile ducts.

C. Physiological function:

i. Secretin maintain the pH of the duodenal contents by regulating gastric acid secretion,

ii. Regulates the secretion of bicarbonate ions and bile into the duodenum from the epithelia lining the pancreatic and biliary ducts.

iii. Inhibits gastric acid secretion, upper intestine motility, oesophageal sphincture pressure via neural pathway,

iv. Induce the secretion of insulin from pancreas.

D. Clinical facts: Excessive or deficient secretion of secretin is not associated with any diseases yet.

6.4 Enteroglucagons

Enteroglucagons are collection of several peptides produced in small intestine mucosal membrane. These peptides structurally and functionally seem like pancreatic glucagons. These are extractable in the large form named as **Glicentin** (69 amino acids). GLP-1 and GLP-2 are also cleaved from the same preprohormone as glicentin. The glucagon gene on chromosome 2q24.2, encodes a large precursor protein Preproglucagon which proteolytically cleaved to form active and inactive peptides. Prohormone convertases digest preproglucagon in different cell and express different expressions. In“Open” type intestinal L cells (also called **EG** cells) prohormone convertases express this gene into GLP-1 and GLP-2 biologically active peptide.

6.4.1. Glucagonlike peptide-1

A. Structure: GLP-1 is composed of 30 amino acids and acts as an incretin. (Incretin hormones are released in response to glucose and increase the ability of the blood glucose to stimulate insulin secretion from the pancreatic islets.)

B. Mode of action: GLP-1 engages a specific G-protein coupled receptor that is present on the beta cells of pancreas where it causes augmentation of glucose-induced insulin secretion. Upon GLP-1 receptor activation, adenylyl cyclase is activated and cAMP generated, leading, in turn, to cAMP-dependent activation of second messenger pathways, such as the PKA and Epac (Exchange protein activation by cAMP) pathways.

C. Physiological function:

i. It promotes insulin expression, delay beta-cell neogenesis, satiety, peripheral glucose disposal, reduces glucagon secretion and beta cell apoptosis.

ii. GLP-1 along with the peptide YY causes ileal brake, in which free fatty acids and carbohydrates in the ileum inhibits gastric emptying through increased secretion of GLP-1 and PYY. This enterogastrone action of GLP-1 further increase the ability to control excessive blood glucose expedition.

D. Clinical facts: GLP-1 based therapies considered as the best treatment for the T2DM patients. The GLP-1 receptor (GLP-1R) is activated directly or indirectly by blood glucose-lowering agents include GLP-1R agonists such as exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide, and langlenatide) and inhibitors (sitagliptin, vildagliptin, saxagliptin, linagliptin, and alogliptin) currently in use for the treatment of type 2 diabetes mellitus (T2DM). The blood glucose-lowering action of GLP-1 is terminated by its enzymatic degradation due to dipeptidyl-peptidase-IV (DPP-IV).

6.4.2. Glucagon-like peptide-2

A. Structure: Glucagon like peptide-2 consisting of 33 amino acids. It is secreted from intestinal mucosa in the presence of unabsorbed nutrients.

B. Physiological functions:

i. GLP-2 has potent tropic effects on intestine; therefore induce mucosal growth and activity of intestinal brush border enzymes.

ii. It delays gastric transit thus increasing nutrient absorption by intestine.

iii. It also has positive effects on glucose transport and may enhance absorptive functions of intestinal villi.

C. Clinical facts: According to the research evidences, human infants in absence of ileum have low GLP-2 level, suffering from Short Bowel Syndrome (SBS). These infants do not show growth in length of the intestine and adaptations throughout the life. These babies either give rise to complications or require transplantation.

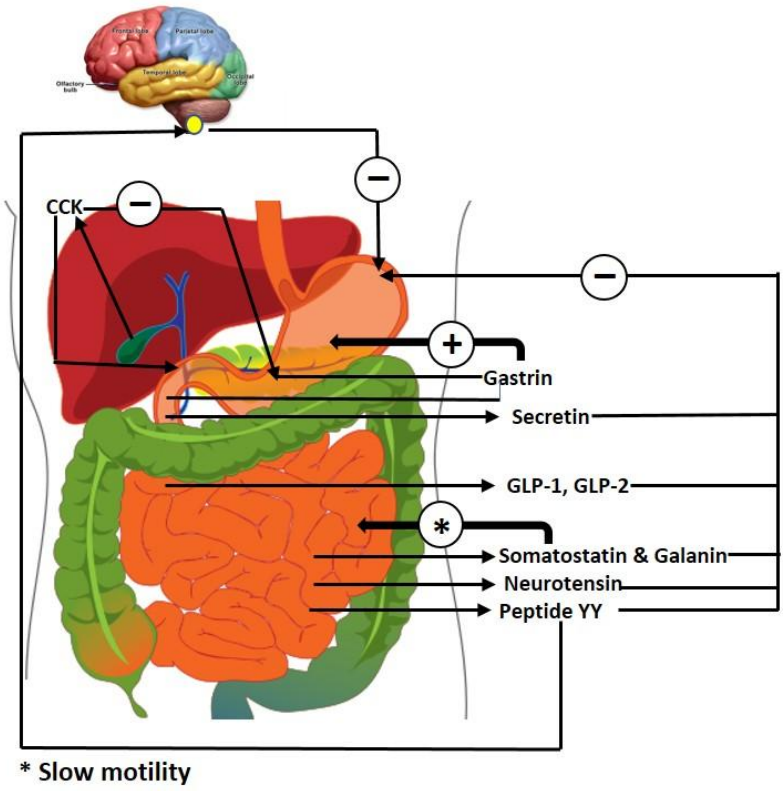

Figure 8: Peptides released from the small intestine inhibit acid secretion and slow processing of food in the stomach. **(Source: Authors)**

6.5 Peptide YY

This hormone is structurally related with pancreatic polypeptide and neuropeptide, consisting of 36 amino acids, secreted by L cells of duodenum, colon and rectum. Luminal nutrients, CCK, GRP, and vagal tone regulate PYY secretion.

A. Structure: The gene for this peptide hormone is located on chromosome number 17q21.31. Peptide YY (PYY), NPY and PP are share considerable amino acid identity

with amidated C-terminal ends. These peptides consist of 36 amino acids, contain several tyrosine residues. PYY circulates as two molecular forms: PYY (1-36) and an N-terminally truncated form, PYY (3-36). PYY has 2 receptors, Y1 and Y2 to exerts its biological actions. PYY (1-36) binds to both Y1 and Y2 receptors, while PYY (3-36) withonly for the Y2 receptor.

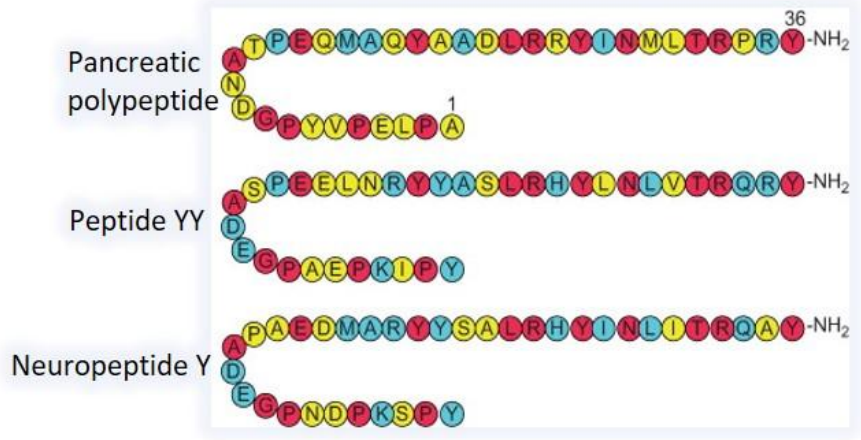

Figure 9: Structure of Pancreatic polypeptide, Peptide YY and Neuropeptide Y.

B. Mode of Action: PYY levels are low in blood in the fasting state but rapidly increase in response to food intake, reach a peak at 1–2 h after a meal and then remain elevated for several hours. Y2 receptors are present throughout the central nervous system, within the nodose ganglion and on vagal afferents. Thus, PYY exerts its feeding effects by acting centrally, via vagal activation or combinations of both.

C. Physiological function:

i. Inhibits gastric acid secretion, motility, gastric emptying, intestinal motility and stop passage of bowel beyond ileum (ileal brake), blood flow and secretion of pancreatic juice.

ii. Suppresses appetite and food intake.

D. Clinical facts: Several research evidences suggested that low circulating PYY concentrations can develop and maintain obesity. Persons with reduced postprandial PYY release exhibit lower satiety and circulating PYY levels that leads to adiposity. In addition, mice lacking PYY are hyperphagic and become obese.

6.6 Neuropeptide Y

Neuropeptide Y (NPY) is primarily synthesized and secreted by neurons in the central and peripheral nervous systems as neurotransmitter. It is presents almost all levels of Gut-Brain and vice-versa axis. In the brain, NPY is expressed in the hypothalamus, cortex, hippocampus, basal forebrain striation, limbic structures, amygdala,and brain stem. In the hypothalamus, it exhibits extremely potent effects on nutrient intake. In the peripheral nervous system, it synthesised by the sympathetic neurons and in the myenteric and submucous plexuses of theenteric nervous system.

A. Structure: The cytogenetic location of the neuropeptide gene is on 7q15.3 chromosome. It is made up of 36 amino acid and structurally related to PYY and PP. NPY exerts its actions via 5 receptor subtypes, including the Y1, Y2, Y4, Y5 and y6 (human pseudogene) receptors. Y1 and Y2 bind to NPY and PYY with similar affinities.NPY and vasoactive intestinal peptide (VIP) are often expressed together in enteric neurons.

B. Mode of action: Its functioning is coupled to pertussis toxin-sensitive Gi/o protein transduction mechanisms.

C. Physiological function:

i. Pancreatic islet cells synthesized and released NPY that inhibits glucose-stimulated insulin secretion via the Y1 receptor.

ii. Increases the blood flow in enteric blood vessels,

iii. Stimulates food intake.

iv. In the gastrointestinal tract, NPY reduces fluid and electrolyte secretion and inhibits both gastric and small intestinal motility.

D. Clinical facts: Patients with pancreatic endocrine tumours, carcinoid tumours, and neurogenic tumours, including neuroblastomas and pheochromocytomas, carry increased circulating NPY level. A research on rats indicated that NPY also play an important role in eating disorders such as obesity indicated by following factors- an increase in glucocortisteroid concentrations in plasma, insensitivity to insulin, mutation of leptin receptor and an increase in NPY mRNA and NPY release. Similarly, experimental evidences on monkey and mice indicated that continuous stress, high fat and sugar diet increased the NYP level which is in turn responsible forabdominal fat belt

formation. In the context of the gut–brain axis, the NPY Y2 receptors occurs in the center/hypothalamus responsible to develop obesity in humans.

6.7 Gastric Inhibitory Peptide (GIP)

It is also known as Glucose dependent insulinotropic polypeptide/Enterogastrone. It is a small polypeptide hormone made up of 42 amino acids, produced in enteroendocrine K cells found mainly in duodenum and proximal jejunum. Along with glucagon like peptide-1, it stimulates insulin secretion. Its working is coupled with G-protein coupled receptors found on the beta cells of pancreas and in small number on few other tissues like bone, brain, stomach, thyroid and adipose tissue.

A. Structure: Gene encoding GIP is located on chromosome 17, which after post-translational processing of the pro-GIP (65 amino acid) by proprotein convertase in K cells, converted into biologically active 42 amino acid long GIP.

B. Mode of action: The GIP receptor is a member of the B-family of G protein-coupled receptors. Its activation results in the stimulation of adenylyl cyclase, Ca^{++}-independent phospholipase A2 and activation of protein kinase A (PKA) and PKC. All are involved in the regulation of beta-cell function.

C. Physiological functions: GIP has an important physiological role as incretin.

- **i.** Maximizes the expression of the anti-apoptotic Bcl-2 and minimises the pro-apoptotic Bax, resulting in reduced beta-cell death.
- **ii.** In adipose tissue, GIP interacts with insulin to increase lipoprotein lipase activity and lipogenesis.
- **iii.** Shows inhibitory effects on gastric acid secretion, gastric emptying and gastrointestinal motility.

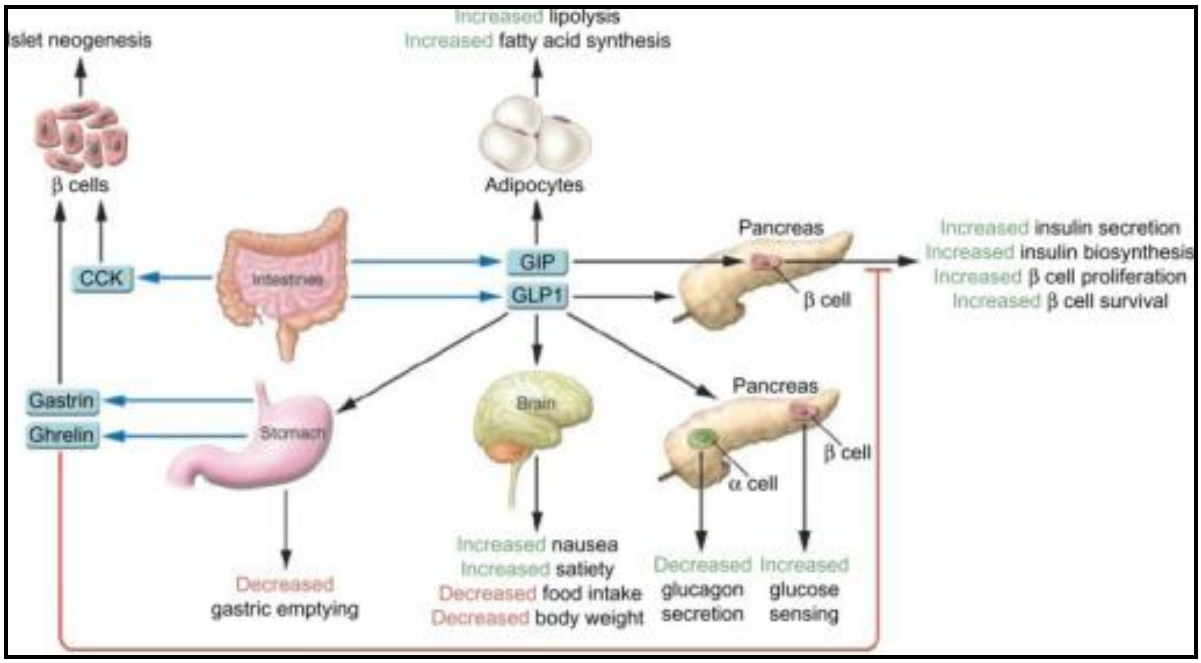

Figure 10: Role of incretin hormones in glucose regulation.

D. Clinical facts: GIP may contribute to the development of food-induced Cushing's syndrome in a subset of patients with adrenal adenomas that express the GIP receptor. Experimental evidences suggested that reduction in GIP production or action can be a strategy to reduce obesity. The meal-dependent nature of GIP release makes K-cells a potential target for genetically engineered production of satiety factors or glucose-lowering agents such as insulin.

6.8 Vasoactive Intestinal Peptide (VIP)

Vasoactive intestinal peptide (VIP) is consisting 28amino acids, belongs to the Secretin family and works as a neuromodulator and neurotransmitter. The gene encoding this peptide resides on chromosome 6q24, widely expressed in the central and peripheral nervoussystems.

A. Structure: VIP produced typically in neurons in intestine. A pyramidal-shaped H-cell found in the small intestine and in the colon of few species also release VIP. VIP is derived from a 170-amino acid precursor molecule with a signal peptide (22 amino acids long) which after processing generates not only VIP but also another similar peptide consisting of 27 amino acids with N-terminal histidine and C-terminal isoleucine termed as **Peptide histidine isoleucine (PHI)**. In human, instead of isoleucine, methionine is

present and termed as **Peptide histidine methionine (PHM).** Although the functional significance of these peptides is unclear.

B. Mode of action: The two closely associated neuroprotective peptides are Vasoactive Intestinal Peptide (VIP) and Pituitary Adenylyl Cyclase-Activating Peptide (PACAP). VIP receptors, VPAC1 and VPAC2 have ability to recognize both VIP and PACAP, as both belong to the same family of GPCRs.

C. Physiological function:

a) Induces relaxation of vascular (Vasodilation) and nonvascular smooth muscle, thus function as an inhibitoryneurotransmitter in GIT.

b) Mediates the relaxation of the lower oesophageal sphincter, the sphincter of Oddi, and the anal sphincter.

c) In humans, VIP and PACAP are co-released as neurotransmitters leading to NO gas regeneration.

d) VIP inhibits gastric acid secretion but stimulates biliary water and bicarbonate, pancreatic enzyme, and intestinal chloride secretion.

e) Regulates release of both insulin and glucagon and exerts either trophic or growth inhibitory effects on both normal and neoplastic cells.

D. Clinical facts: VIPomas (tumours) secrete excessive quantities of VIP, arising from the pancreatic islets or nervous tissue and are associated with chronic, watery diarrhoea.

6.9 Neurotensin

Neurotensin (NT) is a 13amino acid peptide originally isolated in bovine hypothalamus by Carraway and Leeman in 1973. In the gastrointestinal tract, NT generation occurs in N cells of the ileum and in enteric neurons and also produced in the central and peripheral nervous systems where it acts as neurotransmitter and neuromodulators, as well as also secreted from heart, adrenal gland, pancreas, and respiratory tract. Luminal nutrients stimulate NT secretion, especially lipids, but not amino acids or carbohydrates. Gastrin Releasing Peptide (GRP) also stimulates NT release, whereas somatostatin exerts an inhibitory effect.

A. Structure: Neurotensin is a 13-amino acid peptide (tridecapeptide) synthesized by the brain in small amounts and by the N-cells of small intestine and ileum of GITin relatively large quantities. Neurotensin gene is located on 12q21.31 chromosome.

B. Mode of action: Neurotensin mediates its functions by binding to three receptors-neurotensin receptor-1 (NTS-1), NTS-2 and NTS-3, where only NTS-1 and NTS-2 associated with GPCR family. NTS-3 represents a non GPCR protein with NT binding features. NTS-1 is expressed in both the brain and intestine, whereas NTS-2 and NTS-3 are expressed exclusively in the brain. NTS-1 facilitates most of the intestinal responses of neurotensin.

C. Physiological function:

i. Inhibits postprandial gastric acid secretion, pancreatic exocrine secretion, gastric and small intestinal motility.

ii. Stimulates colonic motility and histamine release from mast cells.

iii. Favours fatty acid uptake in the proximal small intestine.

D. Clinical facts: NT acts as potent mitogen, stimulates growth of the colonic epithelium (Colorectal cancer) in vivo. Ulcerative colitis patients have increased number of NTS-1expressing cells significantly in the epithelium and lamina propria of GIT. This modified action of neurotensin can be used in Inflammatory Bowel Disease (IBD), as therapeutic agent. Neurotensin also exhibits antimicrobial activity against bacteria and fungi.

6.10 Motilin

A. Structure: The gene of motilin is situated in the chromosome 13q14.2. Motilin is secreted by M cells of the stomach and small intestine as a 114-amino acid prepromotilin. Circulating motilin levels peak in every 1-2 hours in fasting individuals, in phase with the set of organized contractions that move from the stomach to the ileum which clean the stomach and small intestine from indigestible particles. These contractions are called **Migrating Myoelectric Complex** (MMC).

B. Mode of action: The motilin receptor is a GPCR that accelerate the phospholipase C signalling pathway.

C. Physiological function:

i. Promotes emptying of the stomach and small intestine.

ii. Stimulates gastric and pancreatic enzyme secretion.

iii. Induces contraction of the gallbladder, sphincter of Oddi, and lower oesophageal sphincter.

iv. Accelerates the mixing and propulsive movements of small intestine.

v. Increase the peristalsis in colon.

D. Clinical facts: The motilin receptor also activated by the macrolide antibiotic, erythromycin act as nonpeptide motilin agonists, used in the treatment of delayed gastric emptying also known as **Gastroparesis**. Administration of a low dose of erythromycin will induce a MMC.

6.11 Ghrelin

Ghrelin, a motilin-related peptide, is a 28-amino acid growth hormone releasing factor, synthesized by **Pepithelial cells** in the fundus of **stomach.** It is also produced in smaller amounts in hypothalamus, pituitary, kidney and placenta. Fasting and stressors both induce ghrelin gene expression in the stomach. Ghrelin exhibits gastric prokinetic activity and orexigenic activity following both intracerebroventricular and peripheral administration via the ghrelin receptor expressed in hypothalamic nuclei.

A. Structure: The cytogenetic location of Ghrelin gene is on 3p25.3 chromosome. Ghrelin is synthesized as a preprohormone, then proteolytically processed to yield a 28-amino acid peptide. During synthesis of this hormone, an n-octanoic acid bound to one of its amino acids, which is necessary for its biologic activity.

B. Mode of action: Receptors for this hormone called Growth Hormone Secretagogues Receptor (GHS-R) belongs to G-protein coupled protein, characterized by seven transmembrane spanning helix domains. These receptors are also found in adipose tissue, heart and hypothalamus.

C. Physiological function:

a) Promotes the secretion of growth hormone (GH) via the GHS-R which stimulatessomatotropes (growth hormone synthesizing cells) in anterior pituitary.
b) Induces appetite and food intake by acting via feeding center in hypothalamus.
c) Stimulates gastric emptying.
d) Circulating levels of ghrelinrise and fall before and after food ingestion, indicates its role in appetite regulation.

D. Clinical facts: Obese humans have reduced concentration of ghrelin in blood compare to lean control subjects. Patients with anorexia nervosa have higher than normal plasma

ghrelin levels, which decrease if weight gain occurs. While in Prader-Willi syndrome affected patients, exceptionally high plasma ghrelin concentration in comparison to other obese due to some other cause. Affected persons have developed extreme obesity associated with uncontrollable and voracious appetite. Ghrelin along with rikkunshito (a traditional Japanese herb enhancing acyl ghrelin signalling) are used in the treatment of cancer-related anorexia and cachexia, post-chemotherapy symptoms, rheumatological diseases, age-related frailty etc.

6.12 Somatostatin

Somatostatin was first isolated from the **hypothalamus** and named as **growth hormone-inhibiting hormone.** Later, it is found that the enteroendocrine D cells of stomach also secreted polypeptide somatostatin, composed of 28 amino acids and pancreatic D cells with 14 amino acids. It has short life span of 3 minutes only in circulating blood.

A. **Structure:** Somatostatin hormone transcript is located on 3q27.3 chromosome. The two main types- SST-14 and SST-28are synthesized by proteolytic cleavage of preprosomatostatin into prosomatostatin and finally into mature somatostatin. SST-14 is identical to the hypothalamic tetradecapeptide neurohormone, secreted from pancreas, have two cysteine residues which itself form an internal disulphide bond, whereas SST-28 secreted from the stomach.

B. **Mode of action:** Six somatostatin receptor subtypes (SST-1, SST-2A, SST-2B, SST-3, SST-4 and SST-5) have been identified which all are expressed in duodenum and stomach but pancreatic islets have expressed only SST-2A.All receptors are member of the G protein-coupled receptor superfamily. Each of the receptors activates distinct signalling mechanisms within cells, although all inhibit adenylyl cyclase.

C. **Physiological function:** Somatostatin's actions are generally inhibitory that is, somatostatin inhibits the secretion of growth hormone and thyrotropin in the pituitary, and insulin, glucagon, and PP in the endocrine pancreas.

i. Inhibits the secretion of gut hormones including gastrin, cholecystokinin, secretin, GIP and vasoactive intestinal peptide.

ii. Lowers the rate of gastric emptying, reduces smooth muscle contractions and blood flow within the intestine. Collectively, decreasing the rate of nutrient absorption.

iii. Somatostatin inhibits pancreatic exocrine secretion.

iv. Acts in a paracrine manner on G cells, ECL cells, and parietal cells to inhibit gastric acid secretion.

v. Suppresses pepsin secretion and GIT motility.

D. Clinical facts: Somatostatin plays a physiological role in regulating gastric acid secretion. The lack of the inhibitory function of somatostatin is a causative factor in peptic ulcer disease. The inhibitory properties of somatostatin make it suitable for the treatment of conditions characterized by excess hormone secretion. The longer-acting synthetic somatostatin analogues such as octreotide and lanreotide are useful in the treatment of neuroendocrine tumors, acromegaly, gigantism, gastrointestinal bleeding and portal hypertension by inhibiting the secretion of responsible hormones. Both octreotide and lanreotide are octapeptides bind the SST-2 and SST-5 somatostatin receptors, commonly expressed in neuroendocrine tumours.

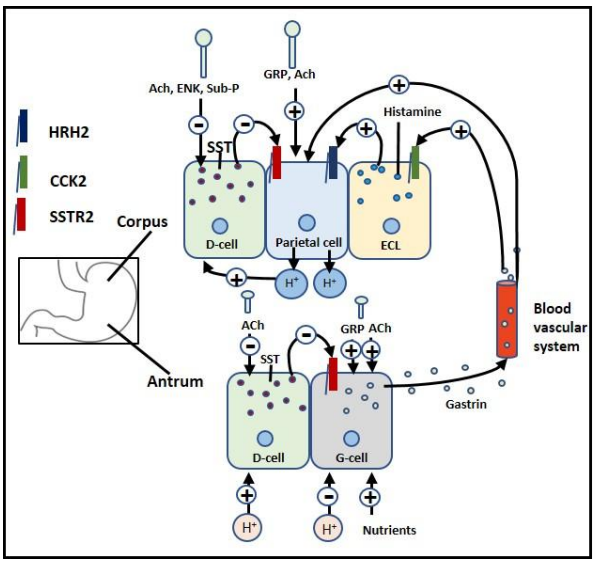

Figure 11: Neurocrine, paracrine and endocrine mechanisms controlling acid secretion from stomach**.** ACh: Acetylcholine, HRH2: Histamine H_2 receptor, SST2: Somatostatin type 2 receptor, ECL: enterochromaffin like cells, GRP: gastrin releasing peptide, ENK: enkecephalins, Sub-P: substance P. **(Source:** Authors**) (Adopted by Norris and Carr)**

6.13 Serotonin

Serotonin is an enteric neurotransmitter.

A. Structure: Serotonin is mainly produced in GIT by enterochromaffin cells. It is synthesized from the tryptophan, which is converted into 5-hydroxy-L-tryptamine (5-HT) or into serotonin in the presence of tryptophan hydroxylase inside the brain andenterochromaffin cells of the intestine. 80-90% of the released serotonin is formed inside the gastrointestinal tract especially by the mucosal lining and myenteric neurons.

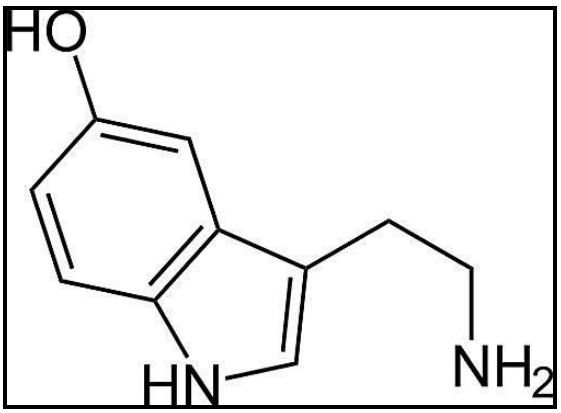

Figure 12: Serotonin Structure

B. Mode of action: The serotonin receptors are based on GPCRs and Ligand gated ion channels. The GPCRs superfamily includes three serotonin receptor families, 5-HT-1, 5-HT-2 and the family including 5-HT-4, 5-HT-6 and 5-HT-7 receptors. The 5-HT-3 receptor is a ligand-gated ion channel and is a separate subfamily. Receptors 5-HT-2, 5-HT-3, 5-HT-4 and 5-HT-7 are present on GI tract.

C. Physiological functions:

i. In GIT, it mainly regulates the bowel peristalsis movement and function.

ii. During meal consumption, it reduces the appetite.

iii. Inhibits gastric acid secretion.

iv. Stimulate the production and secretion of gastric and colonic mucus.

v. Acts directly on mesenteric vascular smooth muscles or by enteric nerves to influence gastrointestinal blood flow.

D. **Clinical facts:** Due to serotonin signalling fluctuations, various diseases can occur inside the GIT including **Irritable Bowel Disease** (IBD) which includes Crohn's Disease, Ulcerative Colitis, and celiac disease and colorectal cancer. Irritable Bowel Syndrome (IBS) has 3 types- with symptoms ranging from diarrhoea (IBS-D), constipation (IBS-C) and alternating (IBS-A), with usual cramping, pain and flatulence. Serotonin concentration increased in diarrhoea and celiac disease but decrease in constipation.

6.14 Histamine

Histamine is synthesized in almost all the tissues of the body, but mainly by the skin, enteroendocrine cells of GIT and lungs. It was discovered in 1899, by Sir Henry Dale and his colleagues at the Wellcome Laboratories. They isolated histamine from the mould ergot.However, in 1927, Best et al. found it in the samples of liver and lungs.

A. **Structure:** Histamine is a small molecule derived from the decarboxylation of the amino acid histidine in the presence of enzyme Histidine decarboxylase and destroyed by the enzyme diamine oxidase (histaminase).

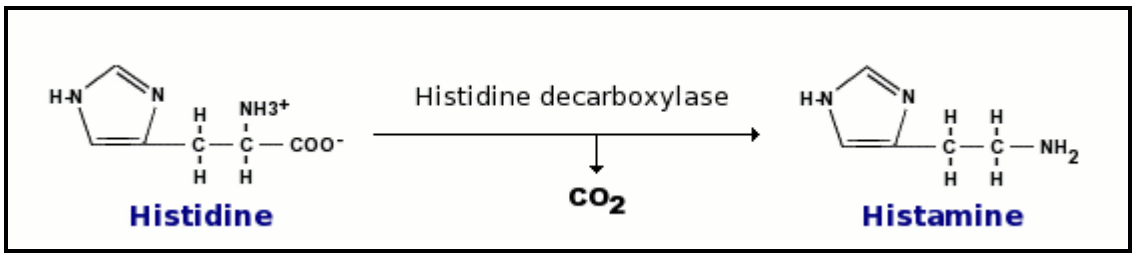

Figure13: Synthesis of Histamine

B. **Mode of action:** Histamine has multiple effects that are mediated by specific surface receptors on target cells. Four types of histamine receptors have now been recognized: H-1, H-2, H-3 and H-4 and all are belonging to GPCRs family. Intestinal tract, especially gastric parietal cells are equipped with H-4 receptors.

C. Physiological function:

i. Important regulator for the acid secretion from the parietal cells of the stomach.

ii. Stimulates contraction and secretion of intestinal tract.

D. Clinical facts: H-4 receptor has a potential therapeutic role of drugs targeting in various GI disorders, such as allergic enteropathy, inflammatory bowel disease (IBD), irritable bowel syndrome (IBS) and cancer.

6.15 Other Hormones

1. Thyrotropin Releasing Hormone (TRH)

Thyrotropin-releasing Hormone is expressed in the entire GIT, including pancreas. In pancreas, TRH secreted and expressed at maximum during perinatal development. Fasting and starvation can reduce TRH release.

A. Structure: TRH is a tripeptide hormone, made up of PyroGlu-His-Proamide, synthesized by the beta cells of pancreatic islets, G-cells of the stomach and neurons of the myenteric plexus of oesophagus, stomach and intestine. In the stomach, histamine and serotonin stimulate and endogenous opioids inhibit TRH release.

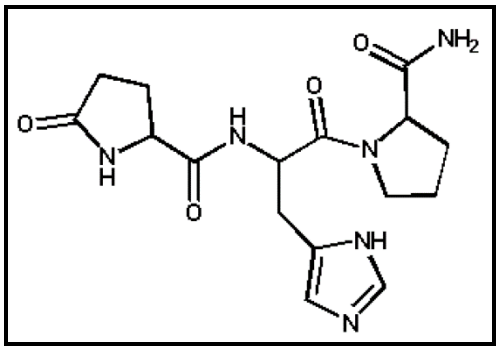

Figure 14: Structure of Thyrotropin Releasing Hormone (TRH)

B. Mode of action: TRH receptors belong to the GPCRs family- TRH receptor 1 (TRHR1) and TRH receptor 2 (TRHR2). TRHR1 is the dominating receptor and primarily mediate the signal transduction by coupling to Gq/11 proteins. Once TRHR1 activates, stimulate phospholipase C, which in turn stimulates inositol 1,4,5-triphosphate (IP3) and 1,2-

diacylglycerol (DAG). These secondary messengers accelerate increase in intracellular calcium and protein kinase activation.

C. Physiological function:

i. TRH suppresses pentagastrin-stimulated gastric acid secretion, serotonin, and blood flow in the gut lining through vagus nerve.

ii. TRH also attenuates CCK-induced gallbladder smooth muscle contraction and inhibits cholesterol synthesis within the intestinal mucosa.

iii. Supresses appetite.

iv. Increases glucagon secretions and inhibits amylase secretion, thus maintain high blood sugar.

D. Clinical facts: Secretion of TRH through vagal nerve can cause stomach cancer and the stomach lining erosion.

2. Pancreatic Polypeptide (PP)

A. Structure: The gene of this polypeptide is located on chromosome 17q21.31. It is a polypeptide consisting of 36 amino acid like NPY and PYY, molecular weight approximately 4,200 Da, produced in PP cells (F-cells) by Islets of Langerhans and small intestine. NPY, PYY and PP share the hairpin fold tertiary structural motif. Its concentration is rapidly increased after meal intake. Its secretion is stimulated by presence of proteins in chime and also secreted in hypoglycaemic, fasting and exercising conditions.

B. Mode of action: Its release and concentration both are mediated by signalling in parasympathetic vagus nerve that turn on the Y4 receptors of NPY.

C. Physiological function:

i. Its main function is action on the exocrine pancreas to inhibit secretion in vivo by acting on receptors in the brain leading to inhibition of vagal output to the pancreas.

ii. PP mainly involved in inhibition of gastrointestinal tract motility, gastric motility, intestinal electrolyte and water secretion.

iii. It slightly increases the basal insulin concentration in plasma without affecting glucose or arginine-stimulated insulin secretion.

D. Clinical facts: Obese children with Prader-Willi syndrome are devoid of PP secretion.

3. Galanin

Galanin is released from the CNS, PNS, pituitary gland, pituitary gland and neural structures of the gut, pancreas. Its gene is present on chromosome 11q13.2. It is secreted from ENS of the gastrointestinal tract in response of intestinal distension, chemical stimulus of mucosa, extrinsic sympathetic neurons, and electrical stimulation of the parietal nerves. Galanin is a C-terminally amidated neuropeptide, was first isolated from porcine intestine with 29amino acid. In humans, galanin is existingin2 molecular forms 19 and 30 amino acids. 3 subtypes of galanin receptors have been identified- GalR1, GalR2 and GalR3, and all are expressed in gastric, intestinal smooth muscles and pancreas. Galanin regulates the food intake and modulation in the neuroendocrine system of the gut. It is reported that galanin may inhibit GIP and GLP-1induced proinsulin gene transcription and insulin secretion, pancreatic exocrine secretion, delays gastric emptying, intestinal ion transport and prolongs colonic transit times and induces the contraction and relaxation of intestinal smooth muscle. It also inhibits the release of acetylcholine from excitatory motor neurons of GIT which in turn influence the gastrointestinal motility.

4. Tachykinins

The tachykinins family includes substance P (SP), neurokinin-A (NKA), and neurokinin-B (NKB) neuropeptide with a common C-terminal pentapeptide sequence essential for their biologic action. All tachykinins are encoded by two genes: a pre-protachykinin-A gene, encodes SP and NKA and a preprotachykinin-B gene that encodes NKB. Tachykinins are synthesized within neurons localized to the submucous and myenteric plexuses, extrinsic sensory fibers, and in enterochromaffin cells in the gut epithelium. Four different tachykinin receptors (NK1 to NK4) have been reported. NK1 receptors preferentially bind to SP, NK2 preferentially binds NKA, and both NK3 and NK4 preferentially bind to NKB.

The tachykinins canregulate vasomotor and gastrointestinal motor activity. Tachykinins exhibit both direct and indirect effects on intestinal smooth muscle contractile activity. NK1 and NK2 receptors on intestinal smooth muscles promote peristalsis, whereas NK3 receptors present on enteric neurons show prokinetic effects. NK1 and NK3 receptors inhibit intestinal motility by increasing the release of NO and VIP which are act as inhibitory molecules.

Tachykinins are commonly produced by gut carcinoids and may be responsible for mediating some of the clinical manifestations associated with these tumours.

7. Summary

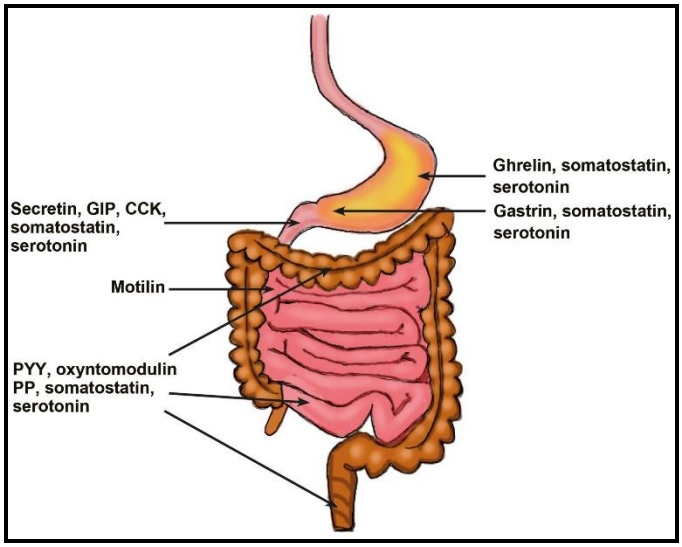

Figure 15: Interaction between gut and its released hormones.

1. The gastrointestinal tract is part of a major physiological system involved in the regulation of the body's energy homeostasis.
2. GIT activities are controlled by hormones releasing from the brain or by GIT itself. The GIT mucosa has enteroendocrine cells, release more than 15 gut hormones which control the GIT activities. These hormones work in association with the enteric nervous system (ENS). The ENS has two components: myenteric (Auerbach) and the submucosal (Meissner) plexuses. The myenteric plexus lies in between the longitudinal and circular smooth muscles and coordinates the contraction and relaxation of intestinal wall. The Meissner plexus is situated in submucosa of the intestinal wall and regulates the gut internal environment, blood flow, epithelial cell functions and secretion.

3. Enteric neurons release neurotransmitters such as acetylcholine, dopamine, serotonin, tachykinins, VIP, NO, GIP, NPY, GRP (Gastrin releasing Peptide), CCK and neuropeptides including Secretin, Galanin, PYY and neurotensin.
4. EECs are based on APUD concept. AUDP cells are a group of cells which originate by a common embryonic neural crest, are ectodermal in nature.
5. In brain, the arcuate nucleus (ARC) of the hypothalamus is play an indispensable role in the regulation of food intake and energy homeostasis. It has two types of neurons with opposing effects for food intake: Orexigenic neurons (stimulating appetite) and Anorexigenic neurons (inhibiting appetite).
6. Gastrin is a synthesized by "Open" type G cells, first appear in the duodenum, further, relocate in antrum and pylorus of the stomach. mRNA transcript of progastrin after cleavage give rise to mature G34 and G17, which are considered as "Classical" gastrin, stimulate gastric acid secretion. Mature gastrin via systemic blood circulation of the body reached to stomach and stimulates the secretion of histamine from Enterochromaffin like cells of gastric fundus which in turn via paracrine diffusion induce acid secretion by binding with histamine-2 receptors located on the oxyntic mucosa and parietal cells. Subsequently, Parietal cells released gastric acid in the stomach.
7. The gene for CCK expressed in the enteroendocrine "Open" type I cells in the duodenum and jejunum, which after release stimulates the secretion of pancreatic digestive enzymes and bile from the gall bladder in response of amino acids and fatty acids in chyme.
8. Secretin is secreted by S cells of the duodenal mucosa in the crypts of Lieberkühn in response to acid in small intestine. It regulates the gastric acid secretion, bile carbonate ions and bile. It also induces the secretion of insulin from pancreas.
9. Enteroglucagon gene is expressed in "Open" type intestinal L cells (also called **EG** cells) where prohormone convertases express this gene into GLP-1 and GLP-2 biologically active peptide. GLP-1 promotes insulin secretion and GLP-2 delayed gastric transit and has tropic effects on intestinal mucosa.

10. Hormones PYY, NPY and PP are share considerable amino acid identity with amidated C-terminal ends. These peptides consist of 36 amino acids, contain several tyrosine residues. PYY inhibits gastric acid secretion, NPY and PP inhibit glucose stimulated insulin secretion.
11. GIP produced in enteroendocrine K cells found mainly in duodenum and proximal jejunum and shows inhibitory effects on gastric acid secretion, gastric emptying and gastrointestinal motility.
12. VIP acts as a neuromodulator and neurotransmitter and inhibits gastric acid secretion as well also induces relaxation of vascular (Vasodilation) and nonvascular smooth muscle, thus function as an inhibitory neurotransmitter in GIT.
13. M cells of the stomach and small intestine secret motilin. Its levels peak in every 1-2 hours in fasting individuals, in phase with the set of organized contractions (called **Migrating Myoelectric Complex**) that move from the stomach to the ileum which clean the stomach and small intestine from indigestible particles. Hence it promotes gastric and intestinal emptying.
14. Ghrelin is synthesized by **Pepithelial cells** in the fundus of **s**tomach. It stimulates gastric emptying and appetite regulation.
15. Enteroendocrine D cells of stomach secrete polypeptide somatostatin. Somatostatin's actions are generally inhibitory, Inhibits the secretion of gut hormones including gastrin, cholecystokinin, secretin, GIP, vasoactive intestinal peptide and pancreatic exocrine secretion.
16. Serotonin, Neurotensin, VIP, PYY and Somatostatin are gastric acid inhibitors, while histamine is important regulator for gastric acid secretion.
17. Motilin, GIP and Ghrelin are promoting gastric emptying.
18. Both serotonin and PYY are appetite suppressors.