

HORMONES AND REGULATORY PEPTIDES OF GASTROINTESTINAL TRACT

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GIT hormones

Gastrin
family:
Gastrin,
CCK

Secretin
family:
Secretin,
Glucagon,
VIP,
GIP

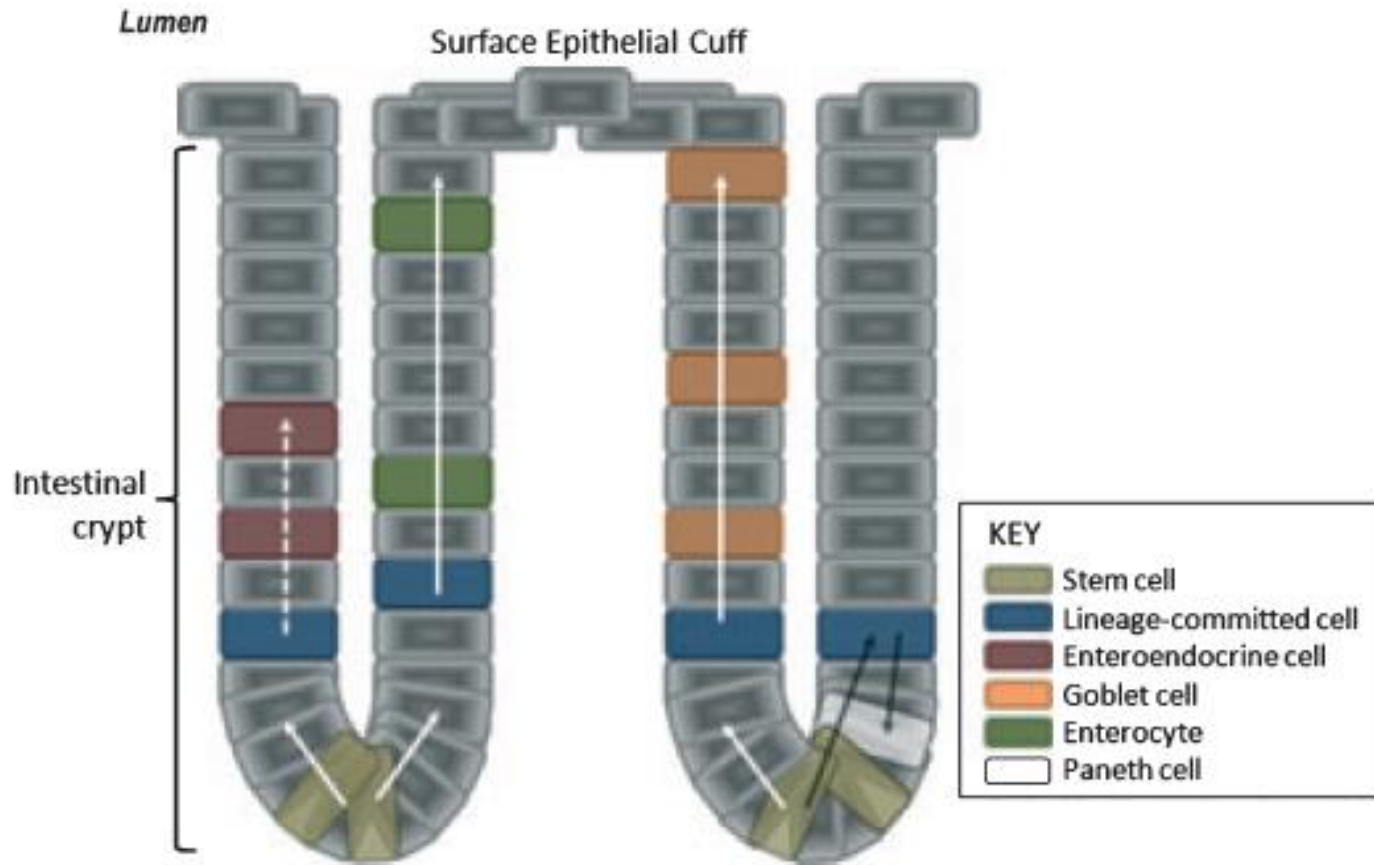
Motilin
family:
Motilin

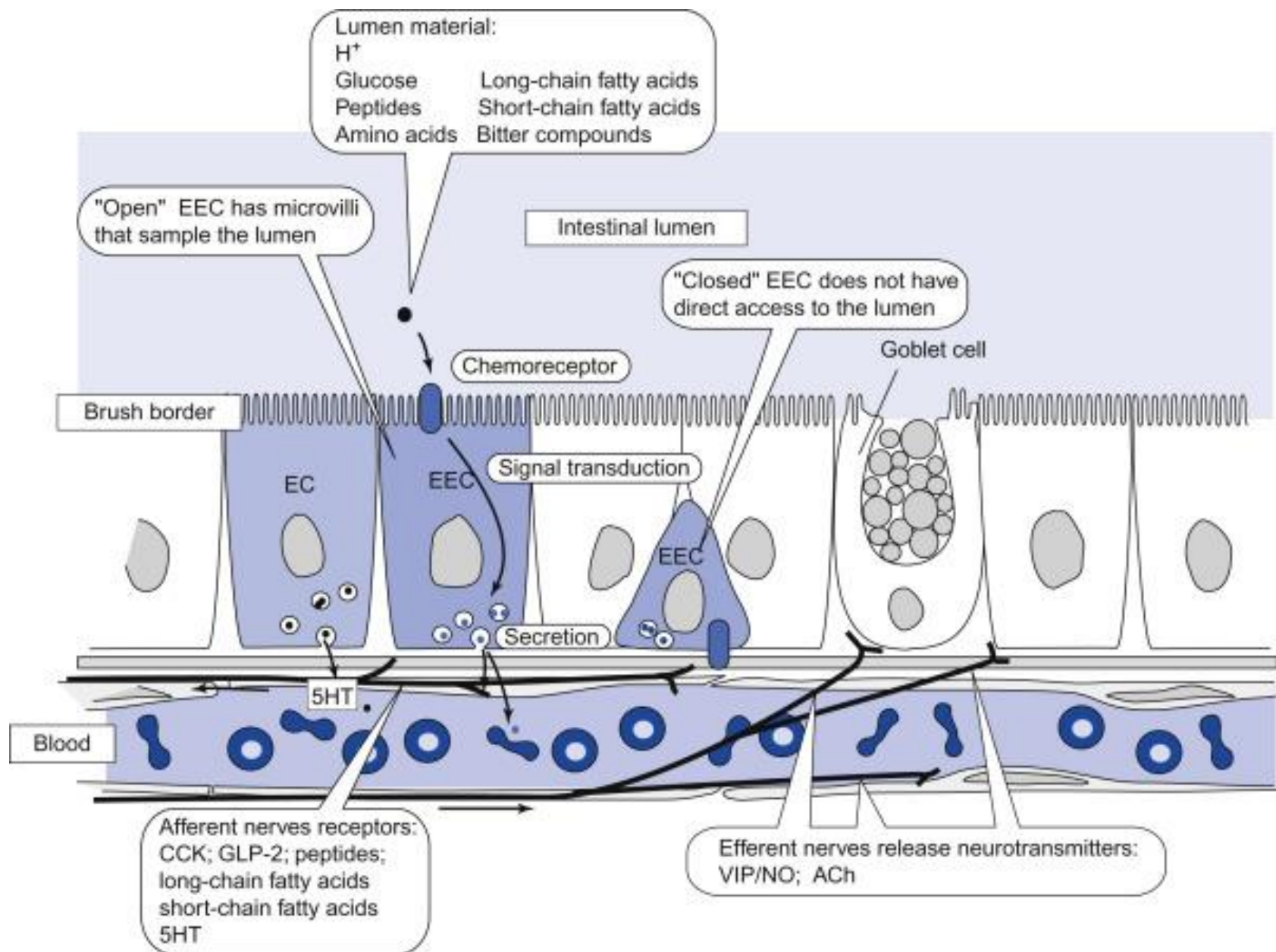
Somatostatin
family:
Somatostatin

Others:
Substance P
Neurotensin
Peptide YY
GRP
Ghrelin

GASTROINTESTINAL HORMONES

- ◉ Enteroendocrine cells - EEC (in epitel of stomach to up to rectum)
- ◉ Enterochromaffin cells - EC





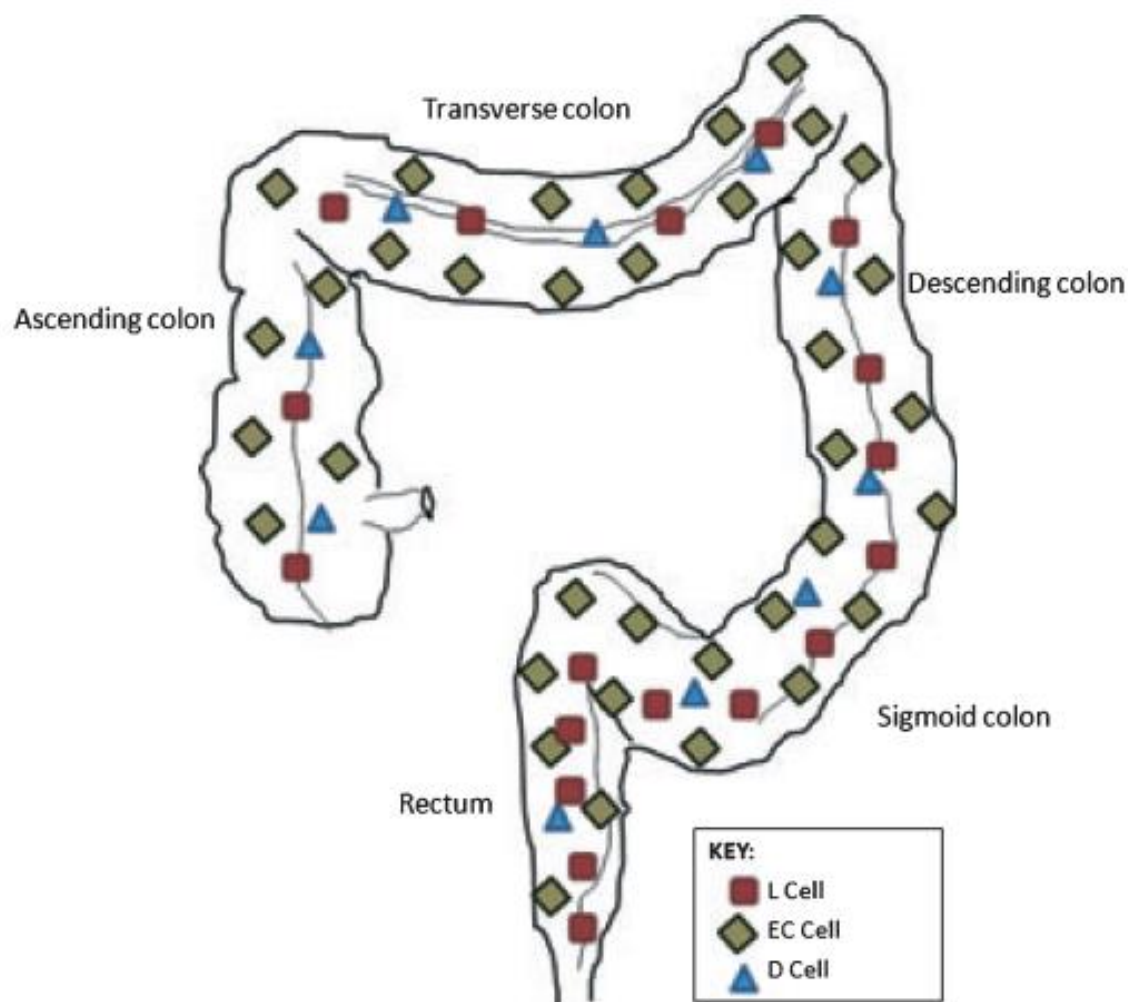


Figure 2 Distribution of enteroendocrine cell subtypes. Enterochromaffin cells are the most abundant enteroendocrine cell subtype of the colon and rectum. D cells are uncommon although scattered evenly throughout the gastrointestinal tract. L cells are uncommon proximal to the terminal ileum, and their frequency increases from proximal to distal being most concentrated in the rectum.

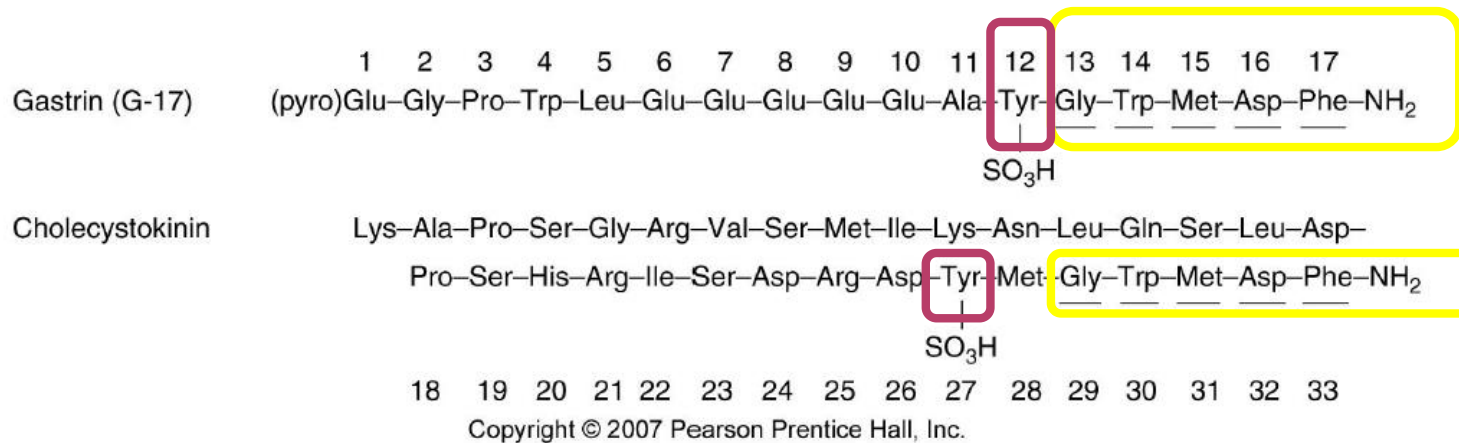
Table 1 Features of EECs of colon and rectum

| Cell type | Distribution | Ultrastructural features | Secretory granules | IHC | Secretory products |
|-----------|---|---|-------------------------|---|--|
| EC cell | Most common EEC type; throughout GIT | Pyramid shaped; often have slender apical process reaching luminal surface | 150–500 nm; pleomorphic | CgA, Syn, 5-HT, TPH | 5-HT |
| D cell | Throughout GIT. Least common EEC type in colon and rectum | Spindle shaped; often have slender apical process and one shorter wider basal extension | 150–300 nm; round | (Syn), somatostatin | Somatostatin |
| L cell | Found in duodenum to rectum; rare before terminal ileum; greatest frequency in rectum | Bottle shaped; often have apical process reaching luminal surface; sometimes have basal process along basement membrane | 200–400 nm; round | (CgA), (Syn), PYY, GLP-1, GLP-2, oxyntomodulin, glicentin | Peptide YY, GLP-1, GLP-2, glicentin, oxyntomodulin |

IHC, immunohistochemistry; EEC, enteroendocrine cell; GIT, gastrointestinal tract; CgA, chromogranin A; Syn, synaptophysin; 5-HT, serotonin; TPH, tryptophan 5-hydroxylase; PYY, peptide YY; GLP-1, glucagon-like peptide 1; GLP-2, glucagon-like peptide 2.

GASTRIN-CHOLECYSTOKININ FAMILY

◉ C-terminal pentapeptide sequence



Gastrin ↑ **HCl**
CCK ↓ **HCl**

AMINO ACID SEQUENCES OF HUMAN GASTRIN - ISOFORMS

| Component ^a | Sequence |
|--|---|
| I Gastrin (big-big gastrin) | Preprogastrin (95 amino acid residues) |
| II Gastrin ₃₄ (big gastrin) | (pyro)Glu-Leu-Gly-Pro-Gln-Gly-His-Pro-Ser-Leu-Val-Ala-Asp-Pro-Ser-Lys-Lys- Glu-Gly-Pro-Trp-Leu-Glu-Glu-Glu-Glu-Glu-Ala-Tyr-Gly-Trp-Met-Asp-Phe-NH ₂ SO ₃ H |
| III Gastrin ₁₇ (little gastrin) | (pyro)Glu-Gly-Pro-Trp-Leu-Glu-Glu-Glu-Glu-Glu-Ala-Tyr-Gly-Trp-Met-Asp-Phe-NH ₂ SO ₃ H |
| IV Gastrin ₁₄ (mini-gastrin) | Trp-Leu-Glu-Glu-Glu-Glu-Glu-Ala-Tyr-Gly-Trp-Met-Asp-Phe-NH ₂ SO ₃ H |

^aGastrin-34, G-17, and G-14 also exist without a sulfate ester at their tyrosyl residue.

GASTRIN

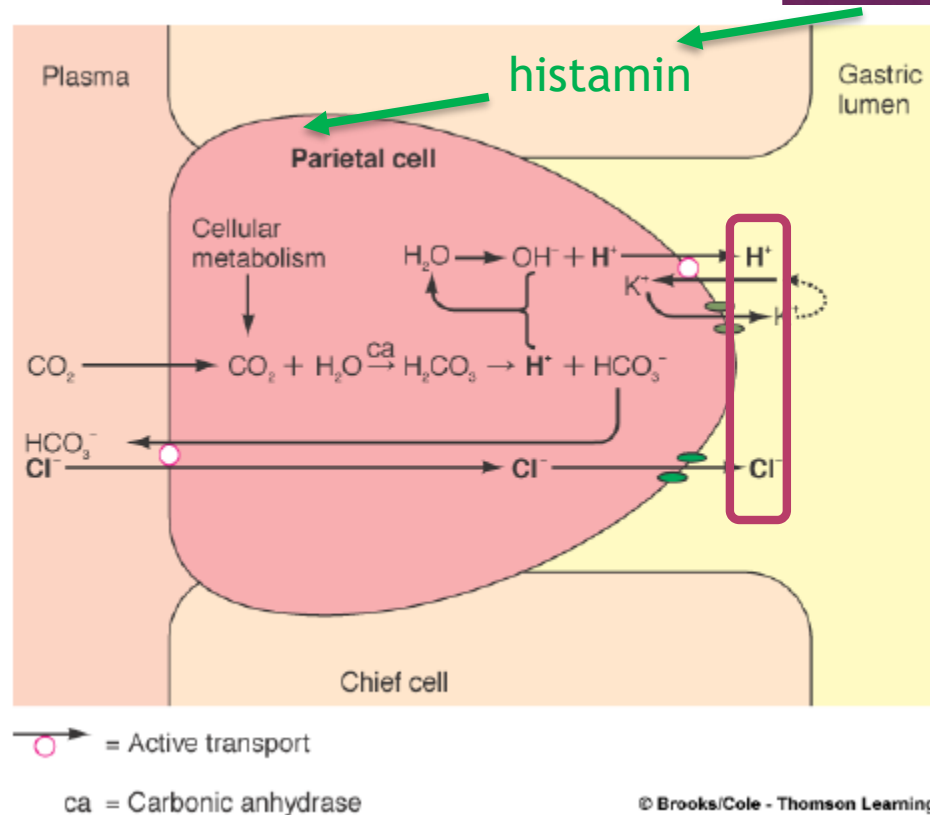
- ◉ Stimulation: presense of protein in stomach
- ◉ Inhibition: somatostatin (D cells), accumulation of acid in stomach ($\text{pH} < 3$)

- ◉ Functions:

- \uparrow HCl and pepsin
- \uparrow motility
- \uparrow insulin
- \uparrow contraction of smooth muscle of the stomach
- \uparrow pancreatic enzymes

- ◉ Hypergastrinemia

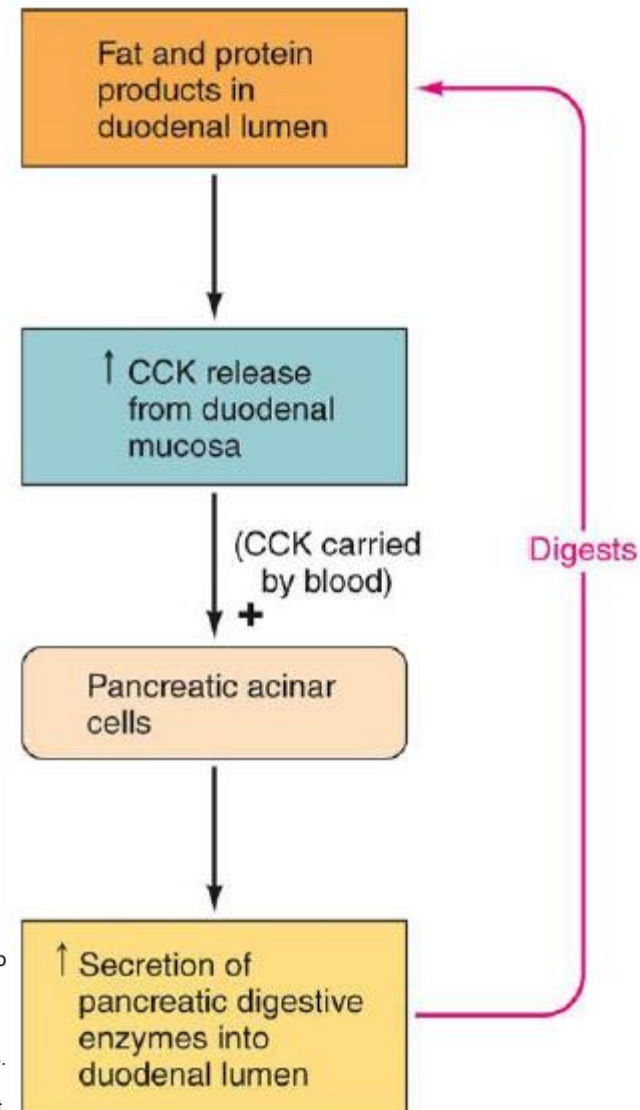
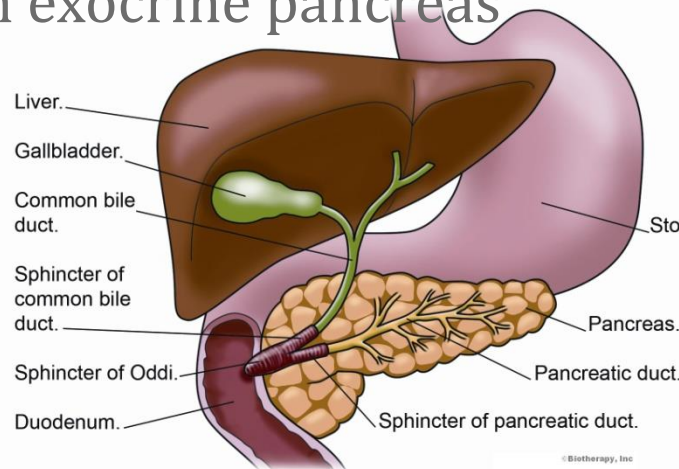
- Zollinger-Ellison syndrome
- neuroendocrine tumors
- proton pump inhibitor



gastrin

CHOLECYSTOKININ

- Production: I cells - duodenum, jejunum
- Stimulation: lipids, proteins
- Functions:
 - ↓ gastric motility and secretion of HCl
 - ↑ contraction of gallbladder
 - relaxation of sphincter of Oddi
 - ↑ pancreatic enzymes
 - trophic effect on exocrine pancreas
 - signaling of satiety

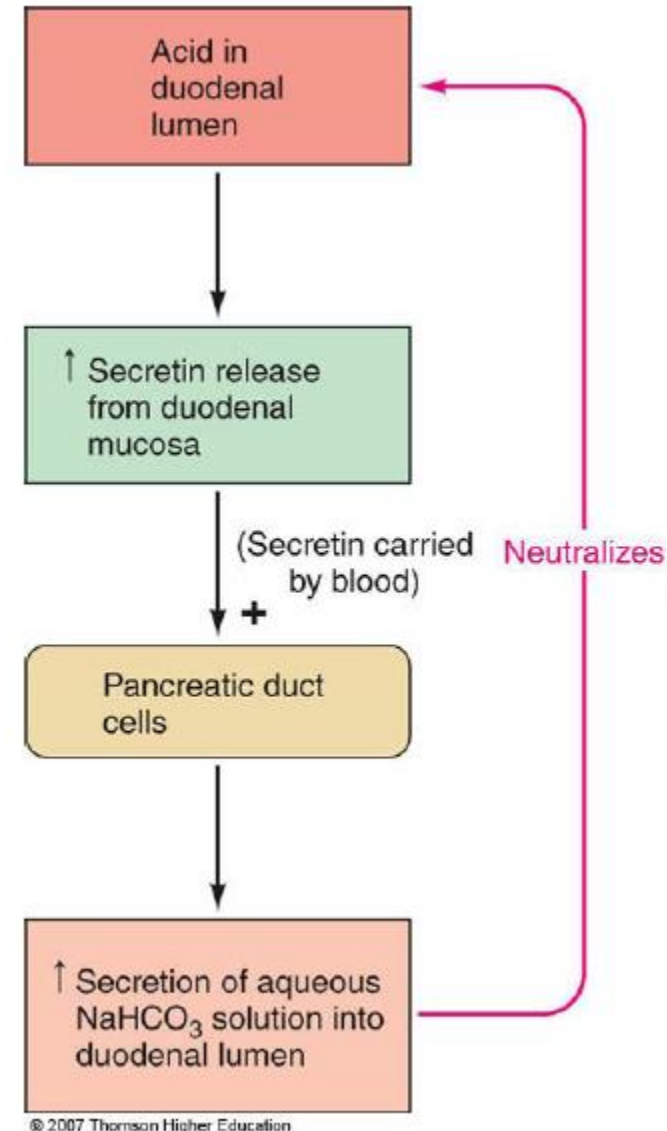
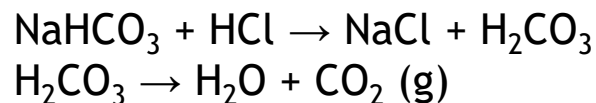


SECRETIN FAMILY

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | |
|----------|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----------------|-----------------|
| VIP | His | Ser | Asp | Ala | Val | Phe | Thr | Asp | Asn | Tyr | Thr | Arg | Leu | Arg | |
| Secretin | His | Ser | Asp | Gly | Thr | Phe | Thr | Ser | Glu | Leu | Ser | Arg | Leu | Arg | |
| Glucagon | His | Ser | Gln | Gly | Thr | Phe | Thr | Ser | Asp | Tyr | Ser | Lys | Tyr | Leu | |
| GIP | Tyr | Ala | Gln | Gly | Thr | Phe | Ile | Ser | Asp | Tyr | Ser | Ile | Ala | Met | |
| | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 |
| | -Lys | Gln | Met | Ala | Val | Lys | Lys | Tyr | Leu | Asn | Ser | Ile | Leu | Asn | NH ₂ |
| | -Asp | Ser | Ala | Arg | Leu | Gln | Arg | Leu | Leu | Gln | Gly | Leu | Val | NH ₂ | |
| | -Asp | Ser | Arg | Arg | Ala | Gln | Asp | Phe | Val | Gln | Trp | Leu | Met | Asp | Thr |
| | -Asp | Lys | Ile | Arg | Gln | Gln | Asp | Phe | Val | Asn | Trp | Leu | Leu | Ala | Gln |
| | -Gln | Thr | Ile | Asn | His | Lys | Trp | Asp | Ser | Lys | Lys | Gly | Lys | Gln | |
| | 43 | 42 | 41 | 40 | 39 | 38 | 37 | 36 | 35 | 34 | 33 | 32 | 31 | 30 | |

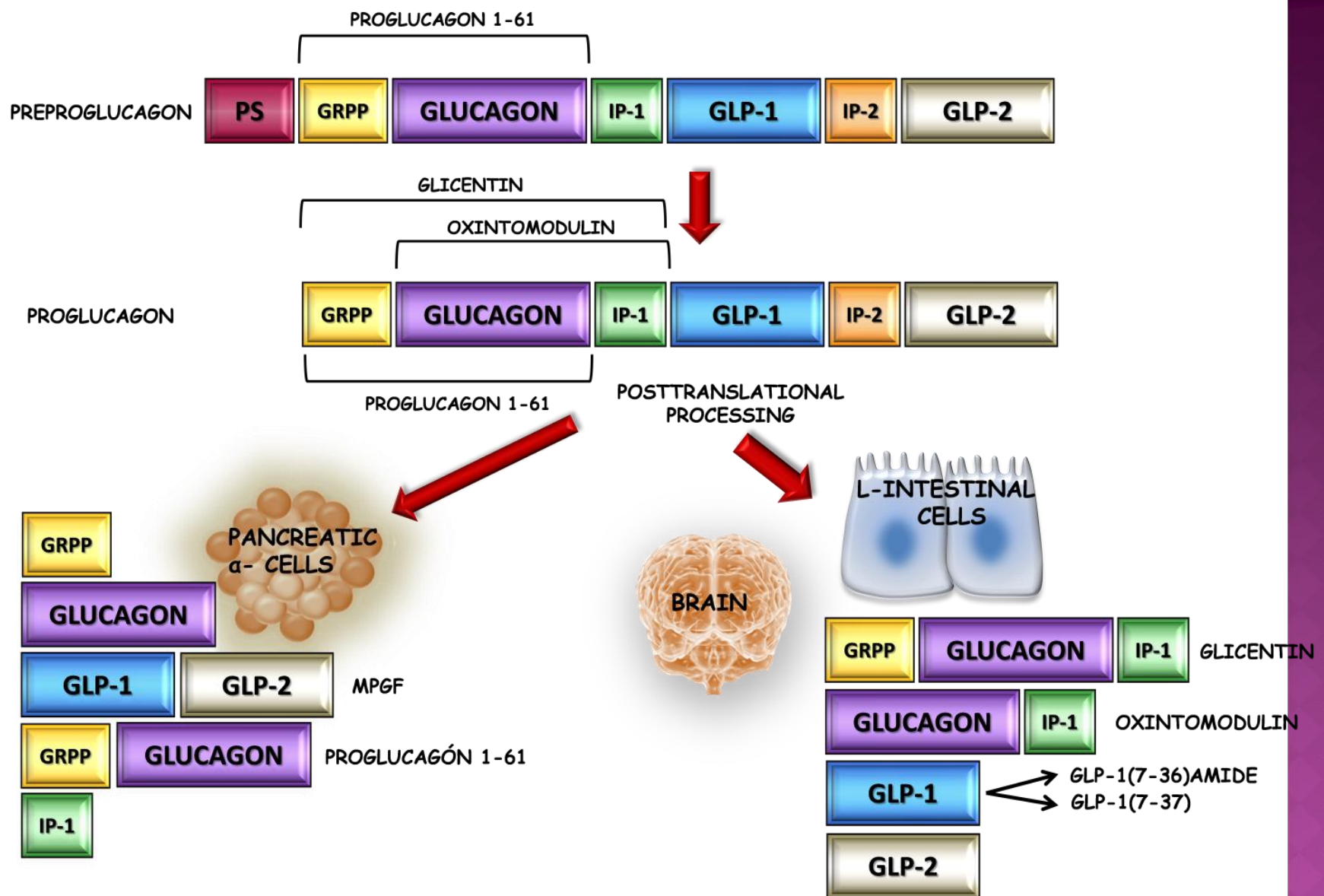
SECRETIN

- ◉ Synthesis: S cells of duodenum and proximal jejunum
- ◉ Stimulation: presense of acid in duodenum (pH<4.5)
- ◉ Functions:
 - ↓ gastric secretion and emptying
 - ↑ NaHCO₃ secretion in pancreas
 - trophic effect on exocrine pancreas like CCK (↑ pancreatic enzymes)
 - central anorectic role - hypothalamus
 - salt-water homeostasis



INTESTINAL GLUCAGON = ENTEROGLUCAGONS AND GLUCAGON-RELATED POLYPEPTIDES (GRPP)

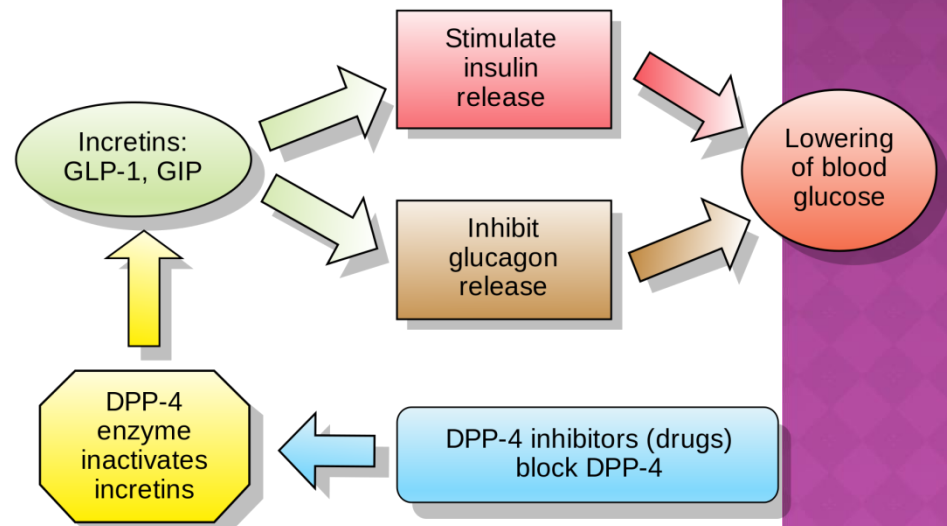
- ◉ **Enteroglucagons:**
- ◉ a peptide hormones derived from preproglucagon
- ◉ **secretion:**
 - mucosal cells primarily of the colon and terminal ileum
- ◉ **release:**
 - when fats and glucose are present in the small intestine
- ◉ **Enteroglucagons:**
 - ↑ insulin secretion
 - ↓ pancreatic glucagon secretion following food consumption
 - ↓ gastric acid secretion ---- delay in stomach emptying



Posttranslational processing of preproglucagon. GLP: Glucagon-like peptide; GRPP: Glicentin-related pancreatic peptide; IP: Intermediate peptide; MPGF: the major proglucagon fragment; PS: Signal peptide.

GLUCAGON-LIKE PEPTIDE-1 (GLP-1)

- a 30 or 31 amino acid long peptide hormone
- derived from proglucagon peptide
- production and secretion after food consumption:
 - intestinal enteroendocrine L-cells
 - certain neurons within the brainstem
- The initial product GLP-1 (1-37) is susceptible to amidation and proteolytic cleavage:
 - 2 biologically active forms:
 - GLP-1 (7-36) amide
 - GLP-1 (7-37) amide
- ↑ insulin secretion
- ↓ glucagon secretion



GLUCAGON-LIKE PEPTIDE-2 (GLP-2)

- ◉ a 33 amino acid peptide
- ◉ GLP-2 is formed by specific post-translational proteolytic cleavage of proglucagon
- ◉ Production after food consumption:
 - intestinal endocrine L cell
 - various neurons in the CNS
- ◉ co-secretion with GLP-1 upon nutrient ingestion.
- ◉ External administration of GLP-2:
 - intestinal growth
 - enhancement of intestinal function
 - reduction in bone breakdown
 - neuroprotection

VASOACTIVE INTESTINAL PEPTIDE (VIP)

- ◉ a peptide hormone that is vasoactive in the intestine
- ◉ Peptide of 28 amino acid residues that belongs to a glucagon/secretin superfamily
- ◉ VIP is produced in many tissues of vertebrates:
 - ◉ gut
 - ◉ pancreas
 - ◉ hypothalamus
 - ◉ lungs....
- ◉ stimulates contractility in the heart
- ◉ stimulates of lipolysis and glycogenolysis
- ◉ causes vasodilatation - lowers arterial blood pressure
- ◉ relaxes the smooth muscle of trachea, stomach and gallbladder
- ◉ ↓ gastric acid secretion
- ◉ ↑ pancreatic electrolyte and water secretion

GASTRIC INHIBITORY PEPTIDE (GIP) = GLUCOSE-DEPENDENT INSULINOTROPIC POLYPEPTIDE

○ Synthesis:

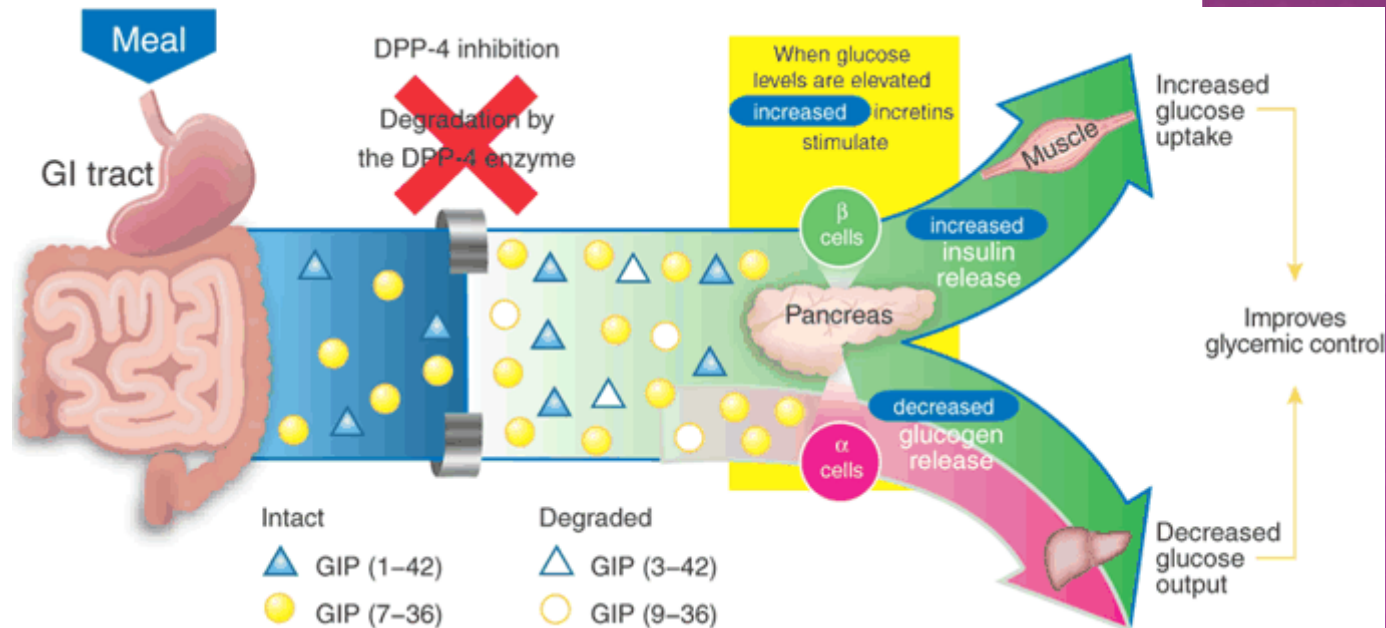
- K cells of duodenum, jejunum, ileum

○ Functions:

- ↓ gastric acid secretion (weak inhibitor)
- ↑ insulin release by pancreas (beta cells) +
- ↓ glucagon (alfa cells)

Production
stimulation:

Glu - 60 min
Fats - 120-150 min



SOMATOSTATIN FAMILY - SOMATOSTATIN

- ◉ = growth hormone-inhibiting hormone (GHIH)
- ◉ peptide hormone (14 amino acids) regulating endocrine system, affecting neurotransmission, cell proliferation - G protein-coupled somatostatin receptors
- ◉ **inhibits insulin and glucagon secretion**
- ◉ Somatostatin has two active forms produced by the alternative cleavage of a single preproprotein:
 - ◉ one consisting of 14 amino acids (SS14)
 - ◉ the other consisting of 28 amino acids (SS28; precursor of SS14)
- ◉ Synthesis:
 - mainly in GIT (in endocrine cells of the stomach)
 - Pancreas - D cells
- ◉ SS inhibits secretion of:
 - Secretin
 - Motilin
 - GIP
 - Insulin
 - Glucagon
 - GH
 - Gastrin
 - Gastric HCl
 - ↓ gastric emptying

MOTILIN FAMILY

MOTILIN

- ◉ a 22-amino acid polypeptide hormone
- ◉ secreted by endocrine Mo cells (or M cells) - duodenum, jejunum, stomach
- ◉ It is released into the general circulation in humans at about 100-min intervals during the inter-digestive state - controls the inter-digestive migrating contractions
- ◉ ↑ gastric activity = GI motility --- "motilin".
- ◉ ↑ gastric emptying

SUBSTANCE P

- ◉ an undecapeptide (a peptide composed of a chain of 11 amino acid residues)
- ◉ the highest concentrations in NS and intestine
- ◉ intestinal smooth muscle contractility
- ◉ normally not released to circulation, just in case of diseases (carcinomas - diarrhea)
- ◉ stimulation of expression of almost all known immunological chemical messengers (cytokines)

NEUROTENSIN

- ◉ a 13 amino acid neuropeptide
- ◉ implicated in the regulation of LH and prolactin release
- ◉ In the CNS = the highest levels in hypothalamus, amygdala and nucleus accumbens
- ◉ It induces a variety of effects:
 - analgesia,
 - hypothermia,
 - higher locomotor activity
 - vasodilation - hypotension
 - smooth muscle contraction
 - ↓ gastric motility and gastric HCl secretion, and peristaltic movement of GIT
 - ↑ pancreatic secretion

PEPTIDE YY

- ◉ also known as **peptide tyrosine tyrosine**
- ◉ Peptide YY is a short (36-amino acid) peptide - EEC cells of small intestine and colon
- ◉ Production: in cells in the ileum and colon in response to feeding.
- ◉ In the blood, gut, and other elements of periphery:
- ◉ **PYY acts to reduce appetite** (similarly, when injected directly into the central nervous system, PYY is also anorexigenic, i.e., it reduces appetite)
- ◉ Dietary fibers from fruits, vegetables, and whole grains - increase the speed of transit of intestinal chyme into the ileum, to raise PYY, and induce satiety.
- ◉ Function:
 - ↓ pancreatic bicarbonate secretion
 - ↓ gallbladder contraction
 - ↓ gastric HCl
 - ↓ intestine motility
 - ↓ gastric emptying

GASTRIN-RELEASING PEPTIDE (GRP) (BOMBEZÍN-SJ)

- ◉ Gastrin-releasing peptide (GRP)
 - ↑ GI hormones
 - ↑ pancreatic secretion
 - ↑ motility
 - ↑ contraction of smooth cells of gallbladder, stomach, duodenum
- ◉ a neuropeptide, a regulatory molecule - regulation of number of physiological and pathophysiological processes.
- ◉ Stimulates the release of gastrin from the G cells of the stomach.

GHRELIN („HUNGER HORMONE“)

- **production:**
- EEC of the GIT: in stomach
- „hunger hormone,, - it increases food intake
- blood levels of ghrelin are highest before meals
- after meal - returns to lower levels
- ↑ gastric acid secretion
- ↑ gastric motility

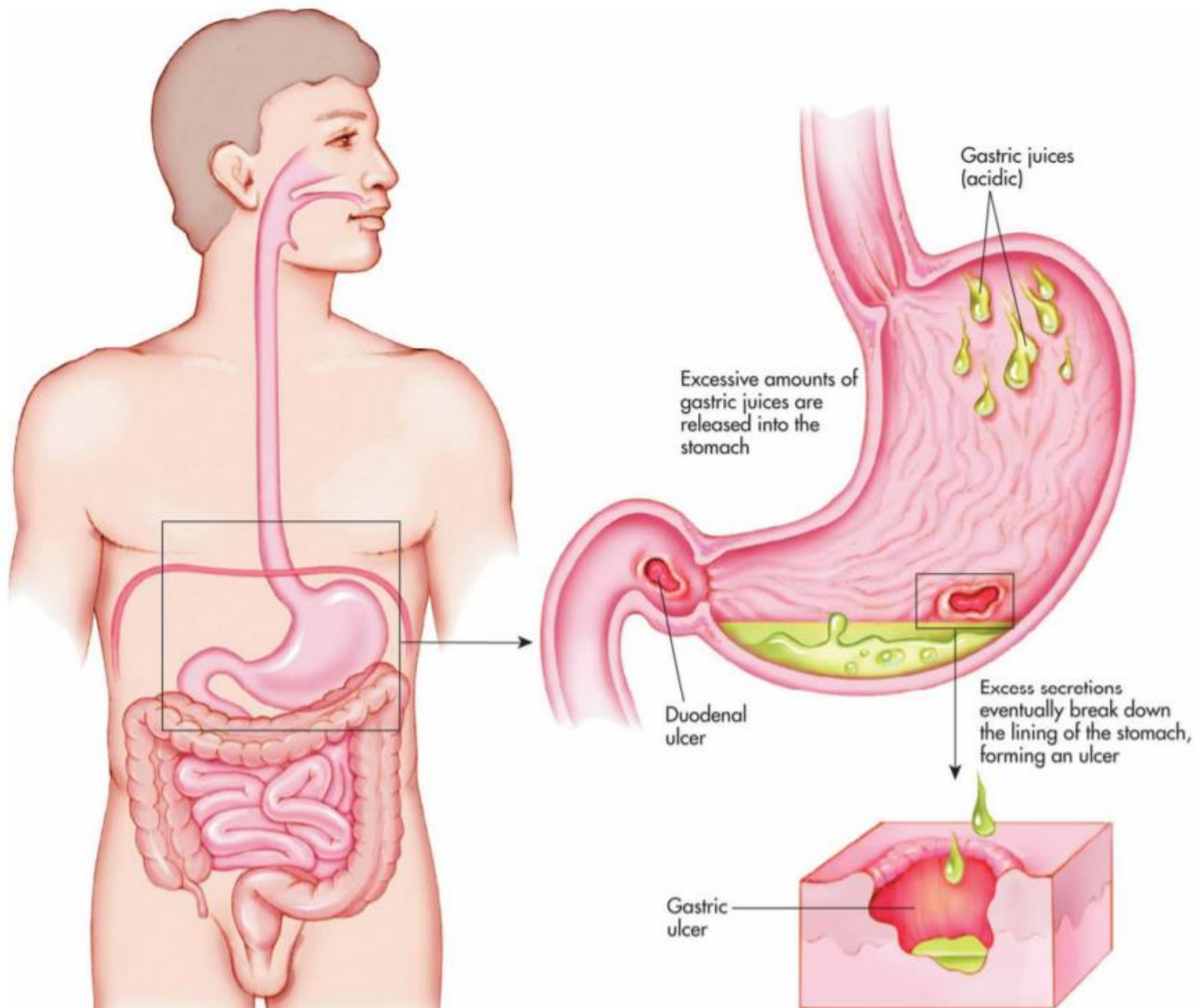
DISEASES OF GASTROINTESTINAL TRACT

- ◉ Peptic ulcers (gastric, duodenal)
- ◉ Hypergastrinemia
- ◉ VIPoma
- ◉ Anorexia nervosa
- ◉ Bulimia nervosa
- ◉ Achalasia

HORMONAL CHANGES IN GIT DISEASES

PEPTIC ULCERS

- ⦿ open sores that develop on the inside lining of stomach and the upper portion of small intestine
- ⦿ the most common symptom - stomach pain
- 1. **Gastric ulcers:** on the inside of the stomach
- 2. **Duodenal ulcers:** on the inside of the upper portion of small intestine (duodenum)



PEPTIC ULCERS - CAUSES

- ◉ Multiple causes:
- ◉ \uparrow HCl secretion \leftarrow increased parietal cell stimulation (e.g. by gastrin in gastrinemia)
- ◉ decreased mucus production (e.g. by aspirin)
- ◉ epithelial cell damage by HCl

- ◉ **the bacteria *Helicobacter pylori***
- ◉ non-steroidal anti-inflammatory drugs (NSAIDs)
- ◉ tobacco smoking
- ◉ stress related mucosal damage

SYMPTOMS AND TREATMENT OF PEPTIC ULCERS

- ◉ Symptoms of a **duodenal ulcer**:
 - waking at night with upper abdominal pain
 - upper abdominal pain that improves with eating
- ◉ Symptoms of a **gastric ulcer**:
 - the pain may worsen with eating
 - pain = a burning or dull ache
 - belching, vomiting, weight loss, or poor appetite

Treatment:

- Diet does not play an important role
- no smoking, stopping use of NSAIDs, stopping alcohol, and taking medications to decrease stomach acid

Table 3. Clinical Presentation of PUD

Typical Symptoms

Epigastric pain
Nausea
Fullness
Bloating
Early satiety
Nocturnal pain

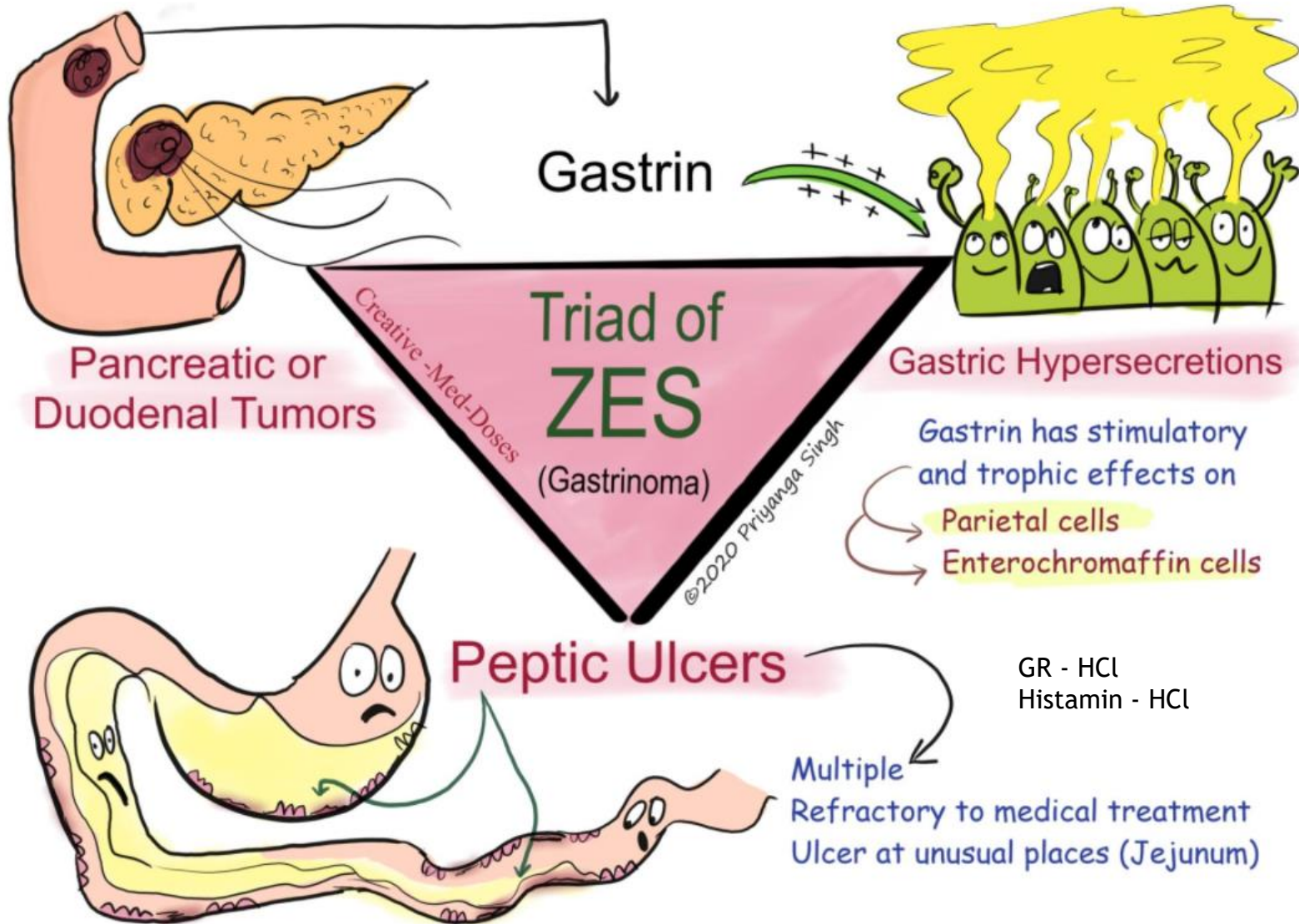
Alarm Symptoms

Anemia
Hematemesis
Melena
Heme-positive stool
Bloody vomiting
Anorexia or weight loss
Persisting upper abdominal pain
radiating to the back
Severe, spreading, upper
abdominal pain

<https://www.youtube.com/watch?v=QZhvJc7PCVI>

HYPERGASTRINEMIA - ZOLLINGER ELLISON SYNDROME (ZES)

- ◉ Cause:
- ◉ Endocrine tumors (gastrinoma) - secretes gastrin →
↑ gastrin in blood (hypergastrinemia) - causing ↑
HCl production by parietal cells of the stomach
- ◉ It leads to peptic ulcers
- ◉ Gastrinomas - mainly in the duodenum, pancreas or stomach.



SYMPTOMS AND TREATMENT OF ZES

- ◉ Chronic diarrhea, including steatorrhea (fatty stools)
- ◉ Pain in the esophagus, especially between and after meals at night
- ◉ Nausea
- ◉ Wheezing
- ◉ Vomiting blood
- ◉ Malnourishment
- ◉ Loss of appetite
- ◉ Malabsorption



- ◉ Treatment:
- ◉ Medicaments - to slow HCl production, surgery (removal of peptic ulcers or tumors)

VIPoma

- ◉ an endocrine tumor
- ◉ overproducing **vasoactive intestinal peptide**
- ◉ about 90% originate from the **non- β islet cells of the pancreas**

Symptoms and signs

- ◉ prolonged watery diarrhea (fasting stool volume > 750 to 1000 mL/day)
- ◉ symptoms of hypokalemia and dehydration
- ◉ lethargy
- ◉ muscle weakness
- ◉ nausea
- ◉ vomiting
- ◉ crampy abdominal pain
- ◉ hypokalemia and impaired glucose tolerance occur in < 50% of patients
- ◉ achlorhydria

VIPoma - TREATMENT

- ⦿ 1st: to correct dehydration:
 - intravenous fluids - to replace fluids lost in diarrhea

- ⦿ 2nd: to slow the diarrhea (medications):
 - Octreotide (a human-made form of the natural hormone somatostatin) - blocks the action of VIP

- ⦿ 3rd: surgical removal of the tumor



ANOREXIA NERVOSA

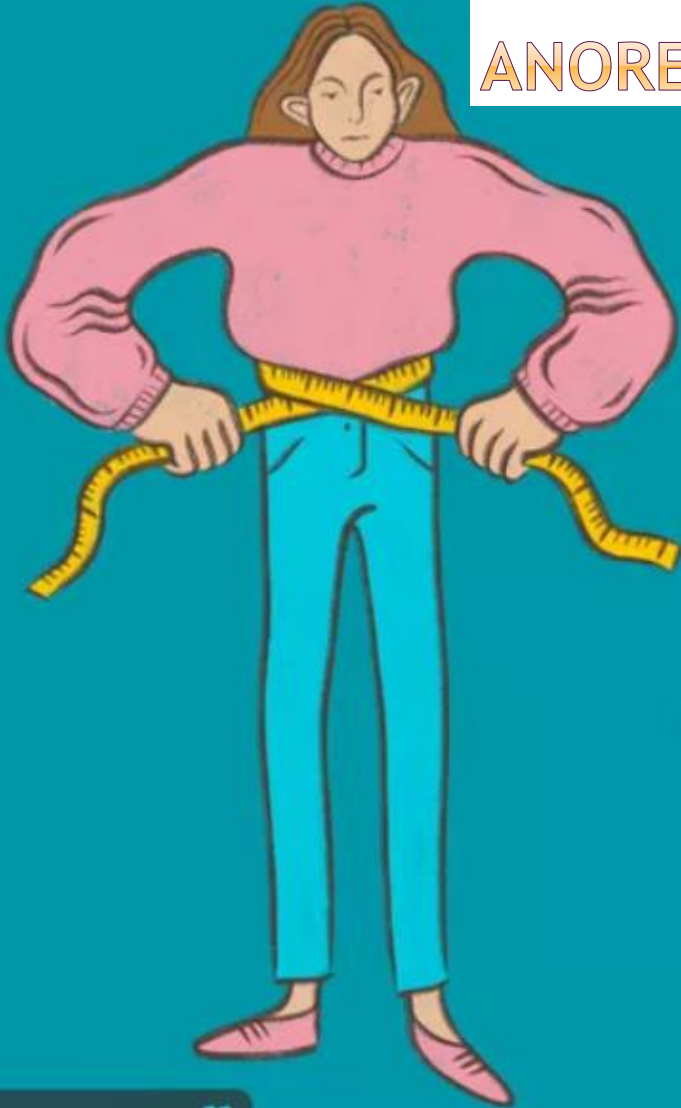
„a loss of appetite,,

- ◉ an eating disorder
- ◉ Characteristics:
 - low body weight
 - restriction of food consumption
 - body image disturbance
 - fear of gaining weight
 - an overpowering desire to be thin
- ◉ the symptom of hunger is frequently presented - its control - a source of satisfaction for the patients

ANOREXIA NERVOSA - CAUSE

- ◉ currently unknown
- ◉ **Genetic factors - is highly heritable**
 - Twin studies: heritability rate 28-58%
 - First-degree relatives of those with anorexia - 12x higher risk of anorexia nervosa
- ◉ **Environmental factors:**
- ◉ **obstetric complications: prenatal and perinatal complications:**
 - preterm birth,
 - maternal anemia,
 - maternal diabetes mellitus,
 - preeclampsia

ANOREXIA NERVOSA - SIGNS, SYMPTOMS



Not maintaining healthy weight



Extreme fear of weight gain



Continuous dieting



Excessive and compulsive exercising



Being obsessed with diets, calories, etc.



Very restricting of what they eat



Avoiding food or denying hunger



Developing rituals regarding food

ANOREXIA NERVOSA AND GIT HORMONES (PEPTIDES)

- report increased fasting total ghrelin levels
- a more rapid and pronounced postprandial rise in CCK in anorexia nervosa patients than in healthy controls

ANOREXIA NERVOSA - TREATMENT

- Treatment - 3 main areas:
 - Restoring the person to a healthy weight
 - Treating the psychological disorders related to the illness
 - Reducing or eliminating behaviors or thoughts that originally led to the disordered eating

BULIMIA NERVOSA



- ◉ an eating disorder
- ◉ Characteristics:
 - binge eating followed by purging
 - excessive concern with body shape and weight
- ◉ To expel the body of calories eaten from the binging phase of the process
- ◉ **Binge eating** = eating a large amount of food in a short amount of time
- ◉ **Purging** = attempt to get rid of the food consumed (vomiting or laxatives)
- ◉ Other efforts to lose weight:
 - Diuretics
 - Water fasting
 - excessive exercise.
- ◉ Vomiting may result in:
 - breakdown of the teeth
 - effects on metabolic rate and caloric intake - thyroid gland dysfunction
- ◉ In general - patients with normal body weight
- ◉ Bulimia is frequently associated with other mental disorders:
 - Depression
 - Anxiety
 - bipolar disorder
 - problems with drugs or alcohol

BULIMIA NERVOSA - CAUSE

- ◉ more common among those who have a close relative with the condition (genetic factors)
- ◉ other risk factors:
 - psychological stress
 - cultural pressure - to attain a certain body type
 - poor self-esteem
 - obesity
- ◉ living in a culture promoting dieting
- ◉ having parents that worry about their weight

BULIMIA NERVOSA - SIGNS, SYMPTOMS



Fear Of Putting On Weight



Mood Changes



Binge Eating



Making Themselves Vomit/Purging



Critical Judgement On Weight & Body Shape



Excessive Exercise After Binge Eating

BULIMIA NERVOSA AND GIT HORMONES (PEPTIDES)

- ◉ Ghrelin levels variable with higher, normal or decreased levels
- ◉ CCK lower (lack of effective assays for measuring)

BULIMIA NERVOSA - TREATMENT

- ◉ Psychosocial treatments
- ◉ Antidepressants



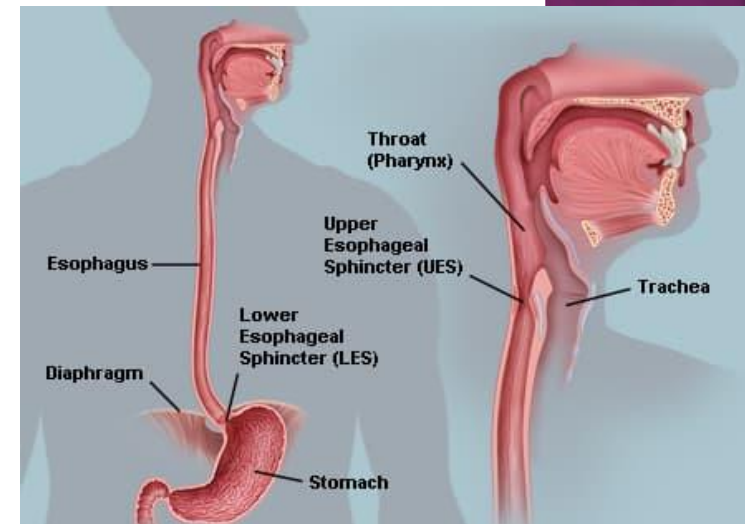
ACHALASIA

Characteristics:

- absent or partial relaxation of the lower esophageal sphincter (→ lower esophageal sphincter to remains closed)
- absence of peristaltic esophageal contraction
- food retention
- esophageal dilation

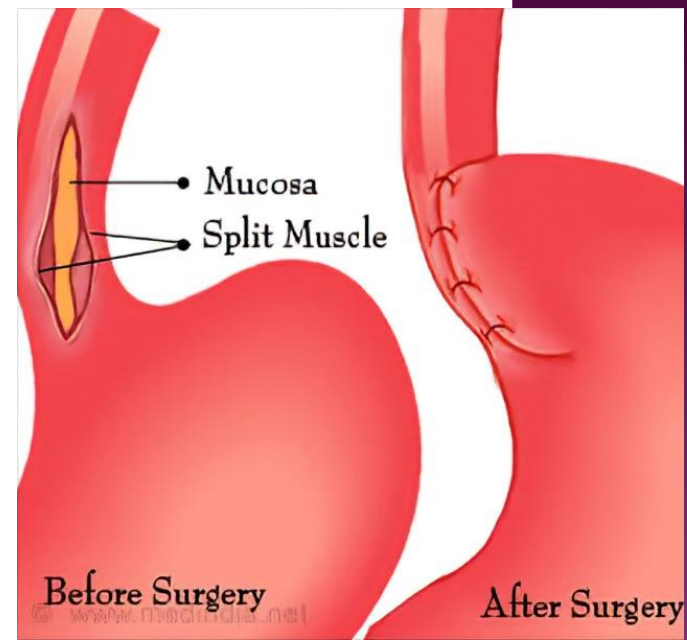
Cause:

- unknown
- primary achalasia (most common) - has no known underlying cause - failure of distal esophageal inhibitory neurons.
- secondary to other conditions - esophageal cancer, Chagas disease (an infectious disease common in South America)



ACHALASIA - SYMPTOMS

1. dysphagia
2. regurgitation
3. heartburn
4. weight loss
5. non-cardiac chest pain



- LES smooth muscle hypersensitivity to gastrin
- ⦿ Diagnosis: esophageal manometry and barium swallow radiographic studies
- ⦿ Treatments:
 - various, but none cures the condition