

Gastric Secretions

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NASPGHAN

Physiology Education Series

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Objectives

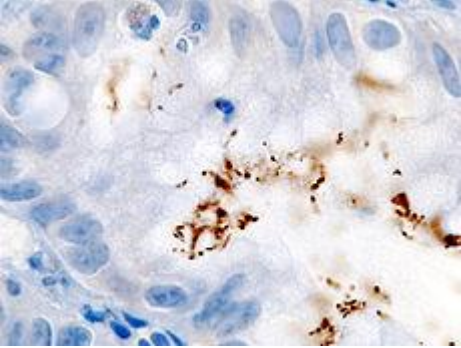
1. Understand the stimuli responsible for the secretion of gastrointestinal hormones
2. Understand the normal gastric secretory processes
3. Know the functions of the gut-derived polypeptides
4. Know the location of hormone-secreting cells in the gastrointestinal tract
5. Understand the mechanism of action responsible for the physiologic effects of various gastrointestinal hormones
6. Understand the process of intracellular hormone processing in the gastrointestinal tract
7. Know how to evaluate gastric secretory processes

Case #1

- 14 yo Mexican American male with 5-6 months of worsening epigastric abdominal pain. 2 days ago the pain worsened and he is now reporting black, tarry stools.
- HR 114 bpm, RR 35 bpm
- Abdomen is tender to palpation in the RUQ and epigastric areas. Bowel sounds are present.

Case #1

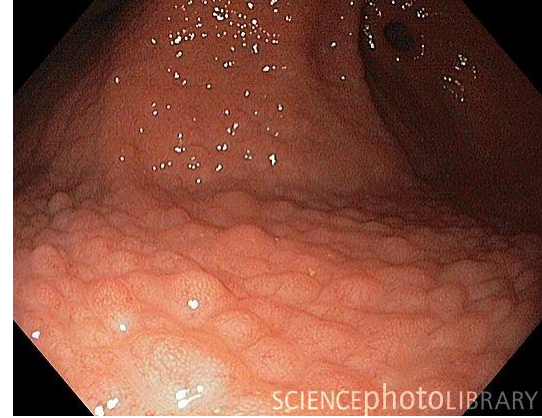
- KUB – Normal
- Hemoccult – Positive
- Stool cultures – Negative
- EGD – Chronic antral gastritis with nodularity and duodenal ulcers visualized
 - Biopsy – Lymphocyte and plasma cell infiltrate in lamina propria with lymphoid follicles.
 - *H. pylori* organisms seen.
- Stool *H. pylori* - Positive



H. pylori

- *H. pylori* colonizes gastric epithelium of 50% of the world's population.
- Complications include:
 - Gastritis
 - Peptic Ulcers
 - Mucosa-associated lymphoid tissue lymphoma (MALT)
 - Gastric cancer

H. pylori

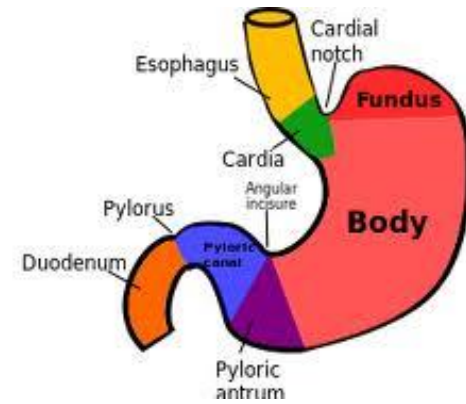


- Acute infection causes hypochlorhydria
- Mechanism for inhibition of acid secretion
 - Pro-inflammatory cytokine interleukin-1 β
 - Suppression of proton pump
 - α -subunit promoter activity
 - Interference in trafficking via tubulovesicles

H. pylori

- Chronic infection
 - Hypochlorhydria vs hyperchlorhydria
 - Antral vs Pangastric involvement

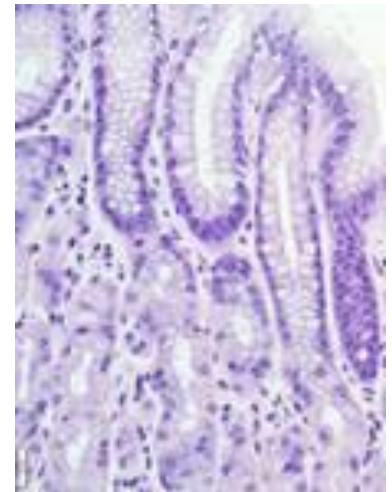
Stomach



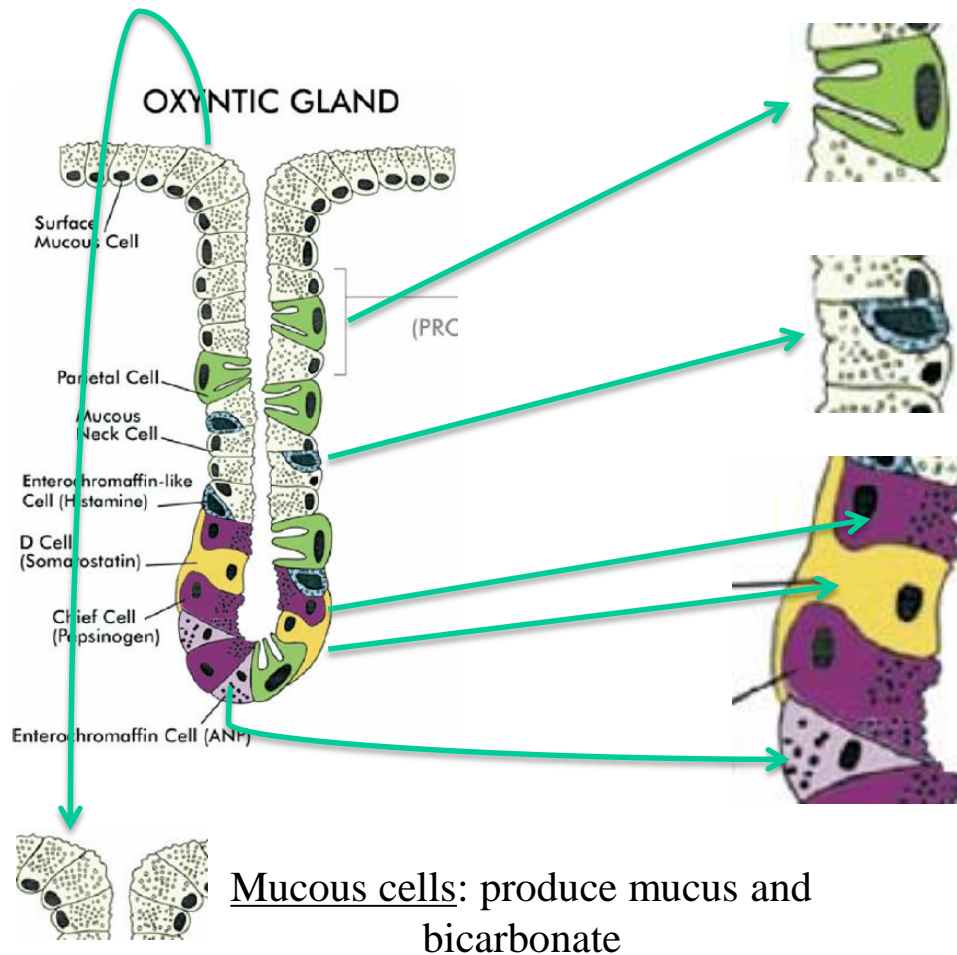
- The stomach is divided into 3 areas
 - fundus, corpus (body), and antrum
- Stomach Function
 - Food and liquid storage
 - Food digestion
 - Delivery of partially digested food to the small intestine

Stomach Epithelium

- Epithelium has glands
 - 2 gland types
 - Oxyntic gland = Parietal cell
 - Body and Fundus (80% of stomach)
 - Pyloric gland = G cell
 - Antrum (20% of stomach)



Oxyntic gland (stomach body and fundus)



Parietal cells: secrete acid

Enterochromaffin-like cells (ECLs):
secrete histamine

Chief cells: secrete pepsinogen and gastric lipase

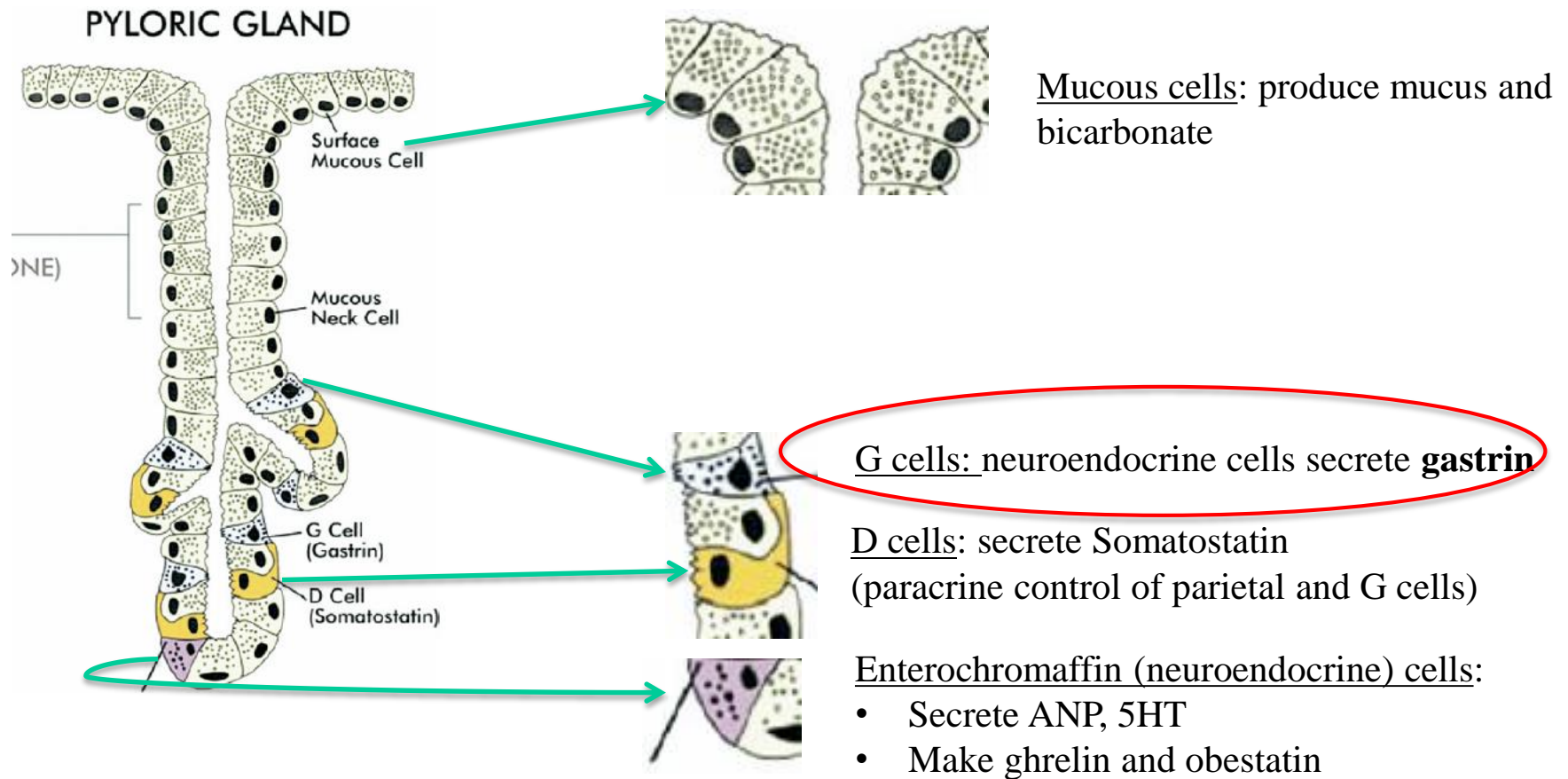
D cells: secrete Somatostatin
(paracrine control of parietal and G cells)

Enterochromaffin cells:

- Contain 5HT and ANP
- Make ghrelin and obestatin

Mucous cells: produce mucus and bicarbonate

Pyloric Gland (antrum and pylorus)



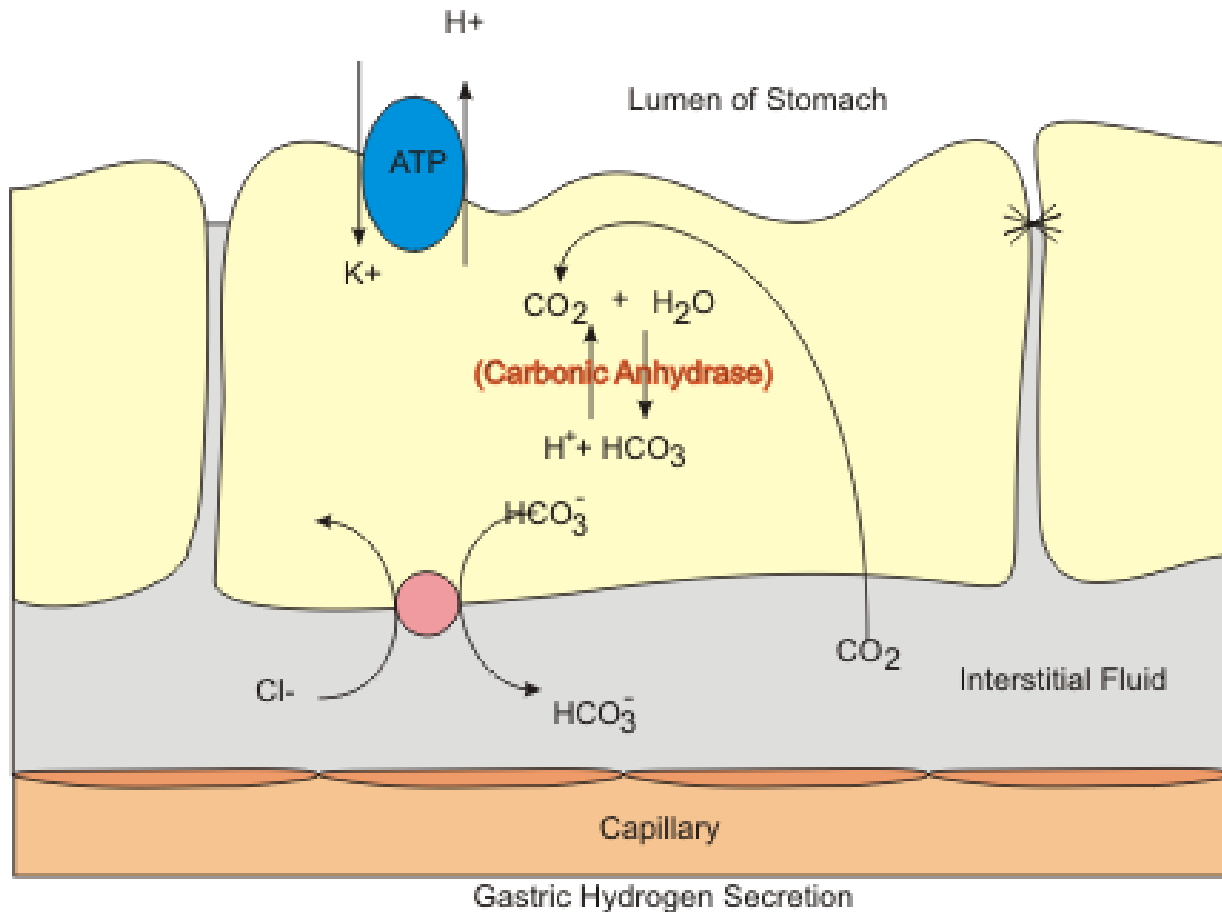
Gastric Secretions

- The stomach secretes:
 - Acid
 - Water
 - Electrolytes
 - Glycoproteins
 - Mucin
 - Intrinsic Factor
 - Enzymes

Gastric Acid

- Gastric acid is necessary for:
 - Protein digestion
 - Absorption of Ca^+ , iron, Vitamin B₁₂ and thyroxin
 - Prevention of bacterial overgrowth and enteric infections
 - Reduction or elimination of food allergenicity(?)
- Gastric acid in excess results in ulceration

Parietal cell acid secretion



Frank Boumphrey M.D.
2009

Control of Acid Secretion

- Balance of Neural, Hormonal and Paracrine pathways
- Activated directly by stimuli from brain
- Reflex activation by stimuli in stomach and intestines
 - Distension
 - Protein/Lipid
 - Acid

Mechanisms of Acid Secretion Control

- **Hormone**
 - Released into blood
 - Reach targets via bloodstream
 - i.e. - Gastrin
- **Paracrine**
 - Released into tissue
 - Reach targets by diffusion
 - i.e. - Histamine and Somatostatin

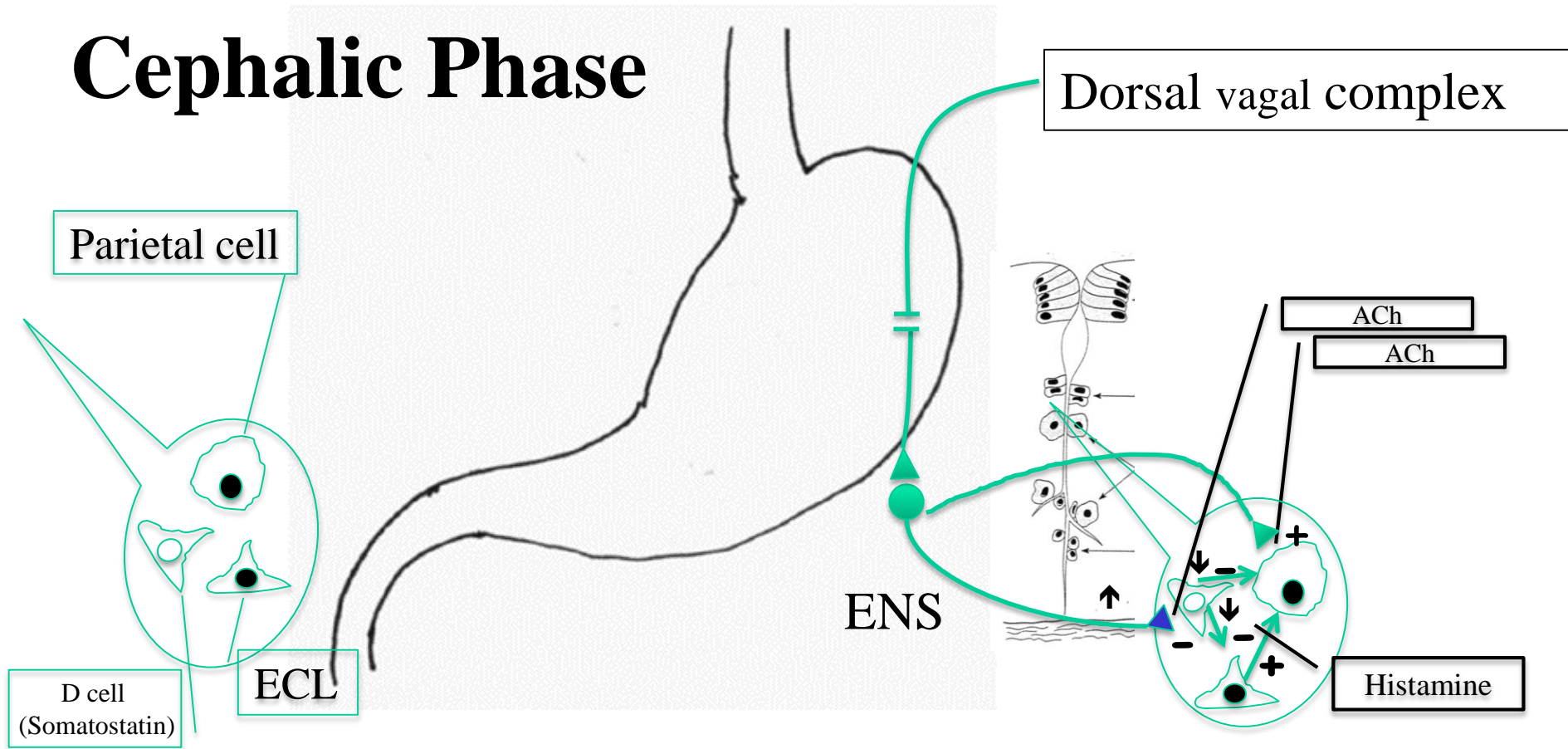
Mechanisms of Acid Secretion Control

- Neurocrine
 - Released from nerve terminals
 - Reach targets by synaptic diffusion
 - i.e. - Acetylcholine and gastrin releasing peptide (GRP)

Stimulation of Acid Secretion

- Three phases
 - Cephalic
 - Gastric
 - Intestinal

Cephalic Phase



FOOD IS COMING

- Smelling or thinking about food
- Pavlov's experiments

Gastric Phase

FOOD HAS JUST ARRIVED

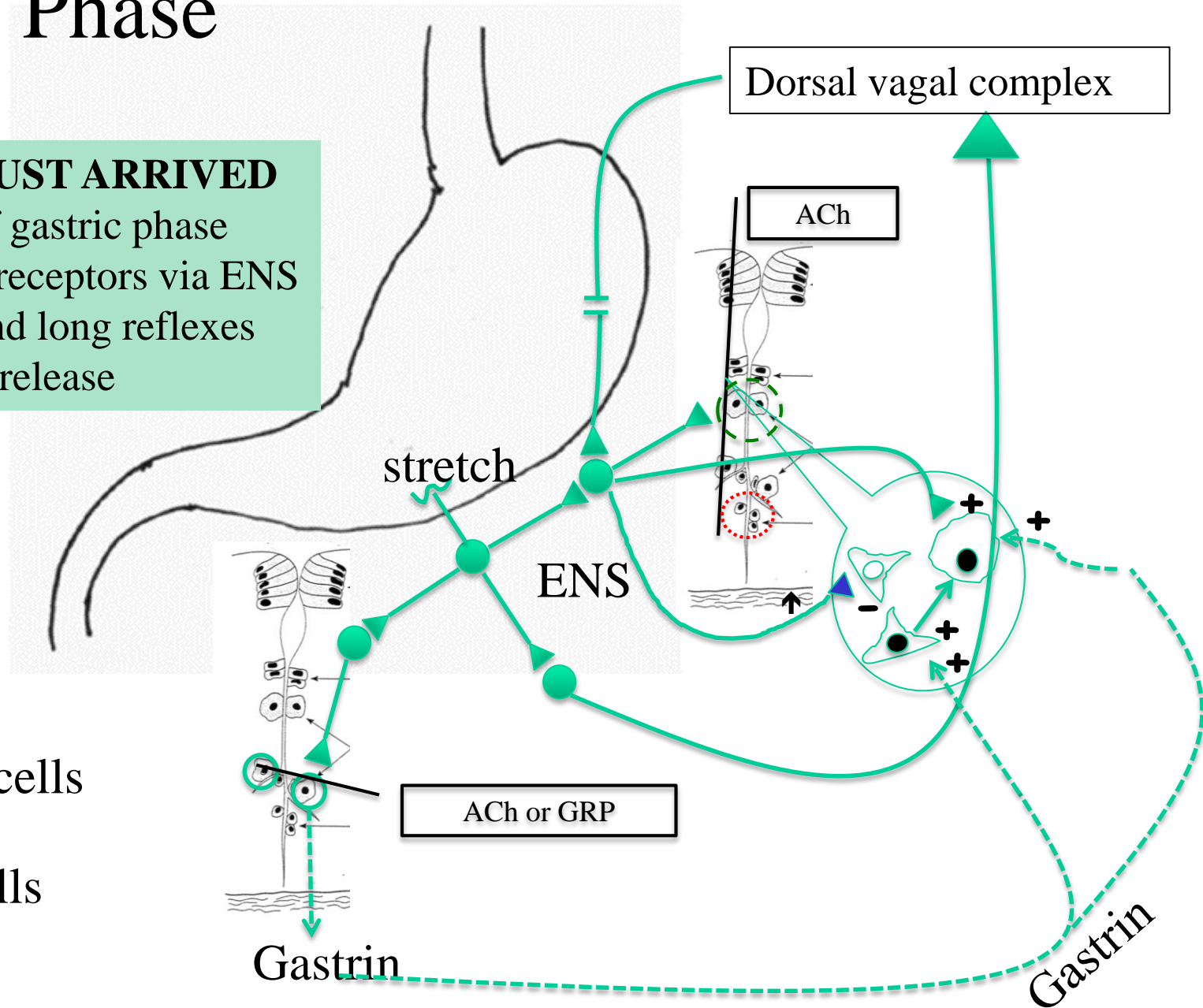
= beginning of gastric phase

- Stretch receptors via ENS
- Short and long reflexes
- Gastrin release

○ Parietal cells

○ G cells

○ Chief cells

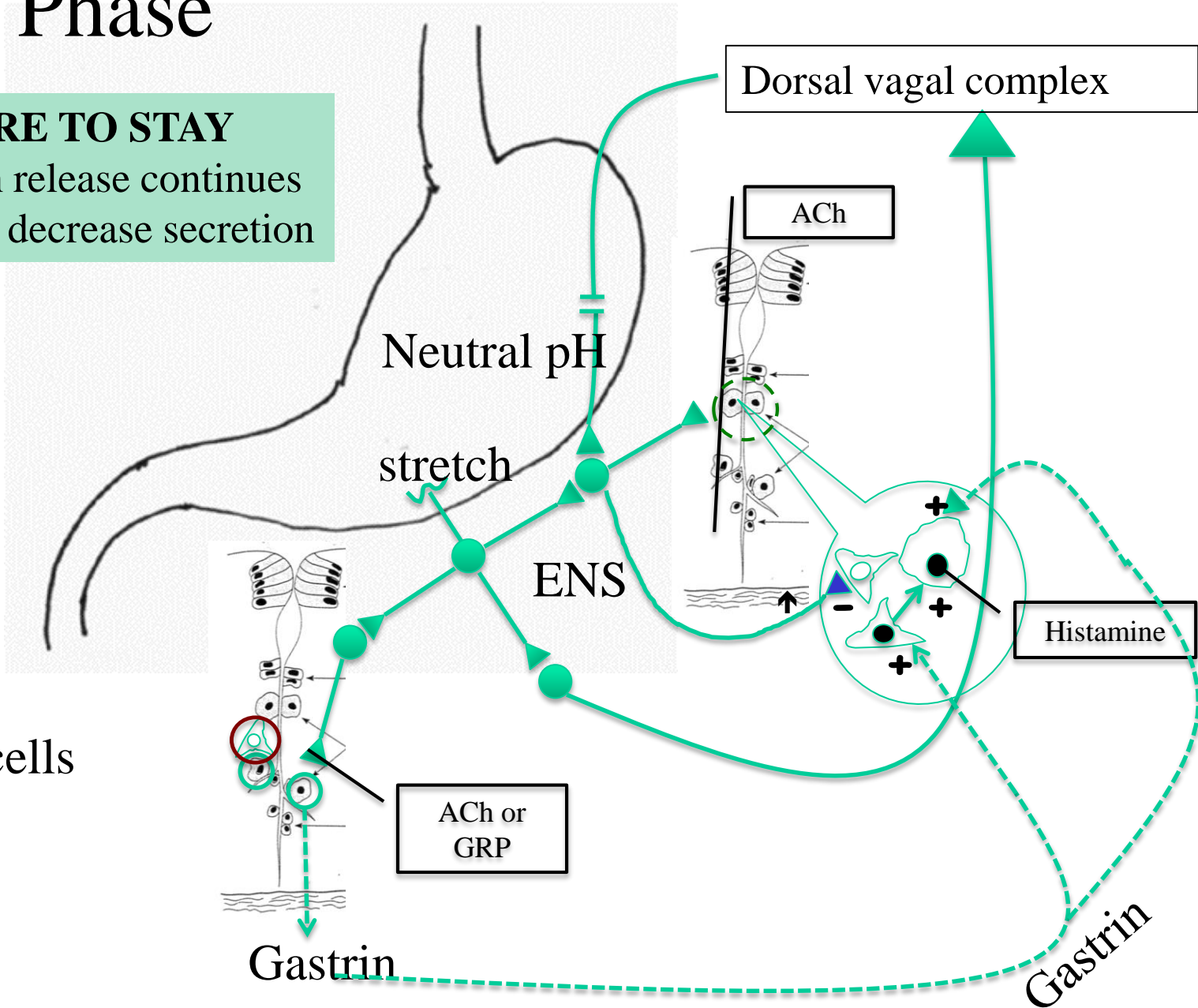


Gastric Phase

FOOD IS HERE TO STAY

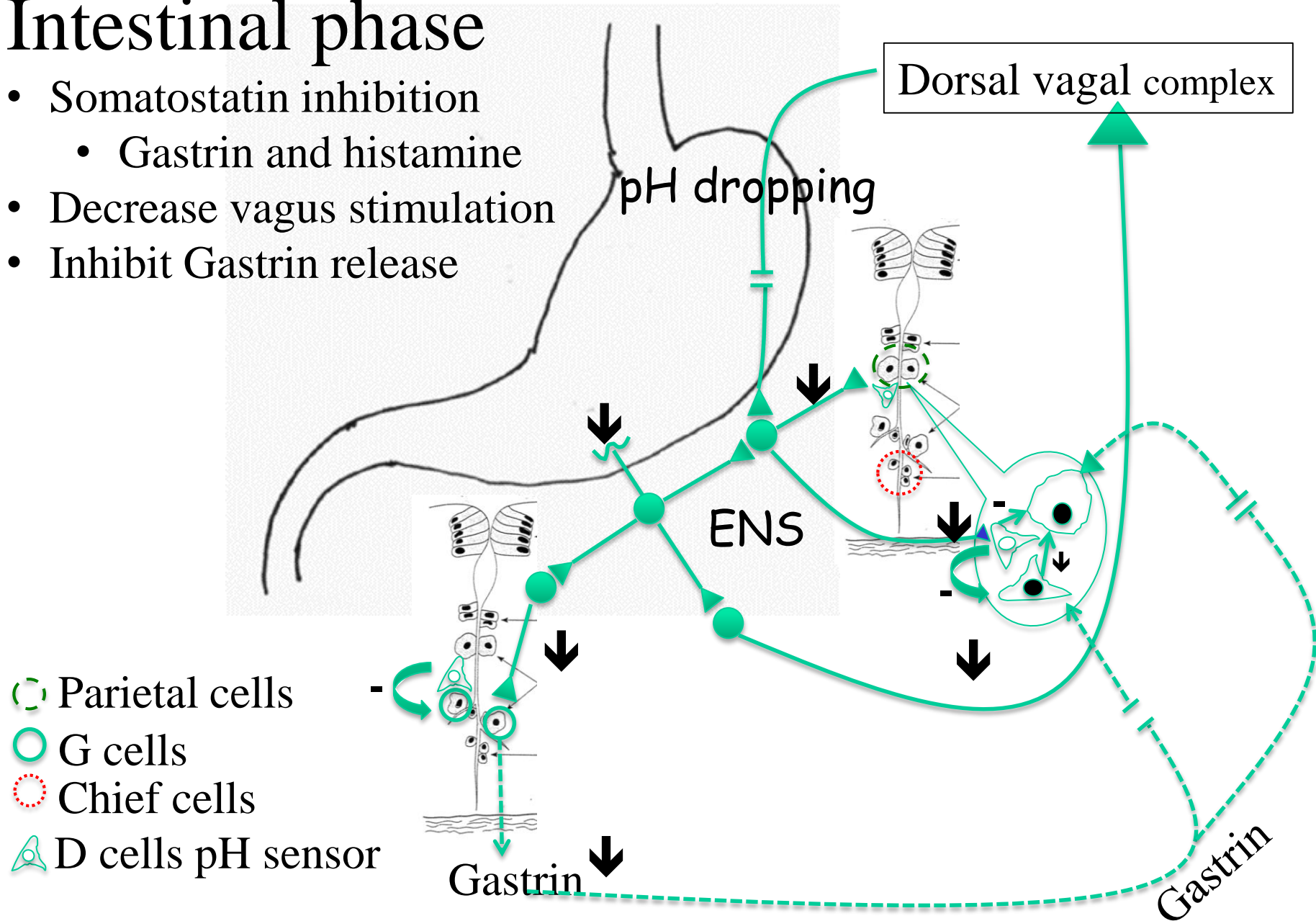
- Gastrin release continues
- D cells decrease secretion

- Parietal cells
- G cells
- D cells



Intestinal phase

- Somatostatin inhibition
 - Gastrin and histamine
- Decrease vagus stimulation
- Inhibit Gastrin release



Hormonal Control of Acid Secretion

- Gastrin
 - Produced mainly by antral G cells
 - Secretion stimulated by
 - Gastric distention
 - AA in lumen
 - Stimulates gastric acid secretion during meal ingestion
 - **Direct stimulation of parietal cells** via CCK-2 receptor
 - Indirect stimulation of parietal cells via enterochromaffin-like cells (ECLs).
 - Histamine released when stimulated by Gastrin
 - Activates parietal cell H₂ receptors

Paracrine Control of Acid Secretion

- Histamine
 - Stimulates acid secretion
 - Stored in ECLs in the basal half of the oxyntic gland
 - Gastrin stimulates histamine release from ECLs
 - Histamine binds to the H₂ receptor on parietal cells leading to activation of proton pump.
 - Secretion increased by gastrin, aspirin, indomethacin, dexamethasone, IL-1, and TNF

Paracrine Control of Acid Secretion

- Somatostatin
 - Inhibits acid secretion
 - Released from D cells
 - Direct inhibition of parietal cells
 - Indirect inhibition
 - Decrease histamine secretion from ECLs
 - Decrease gastrin secretion from G cells

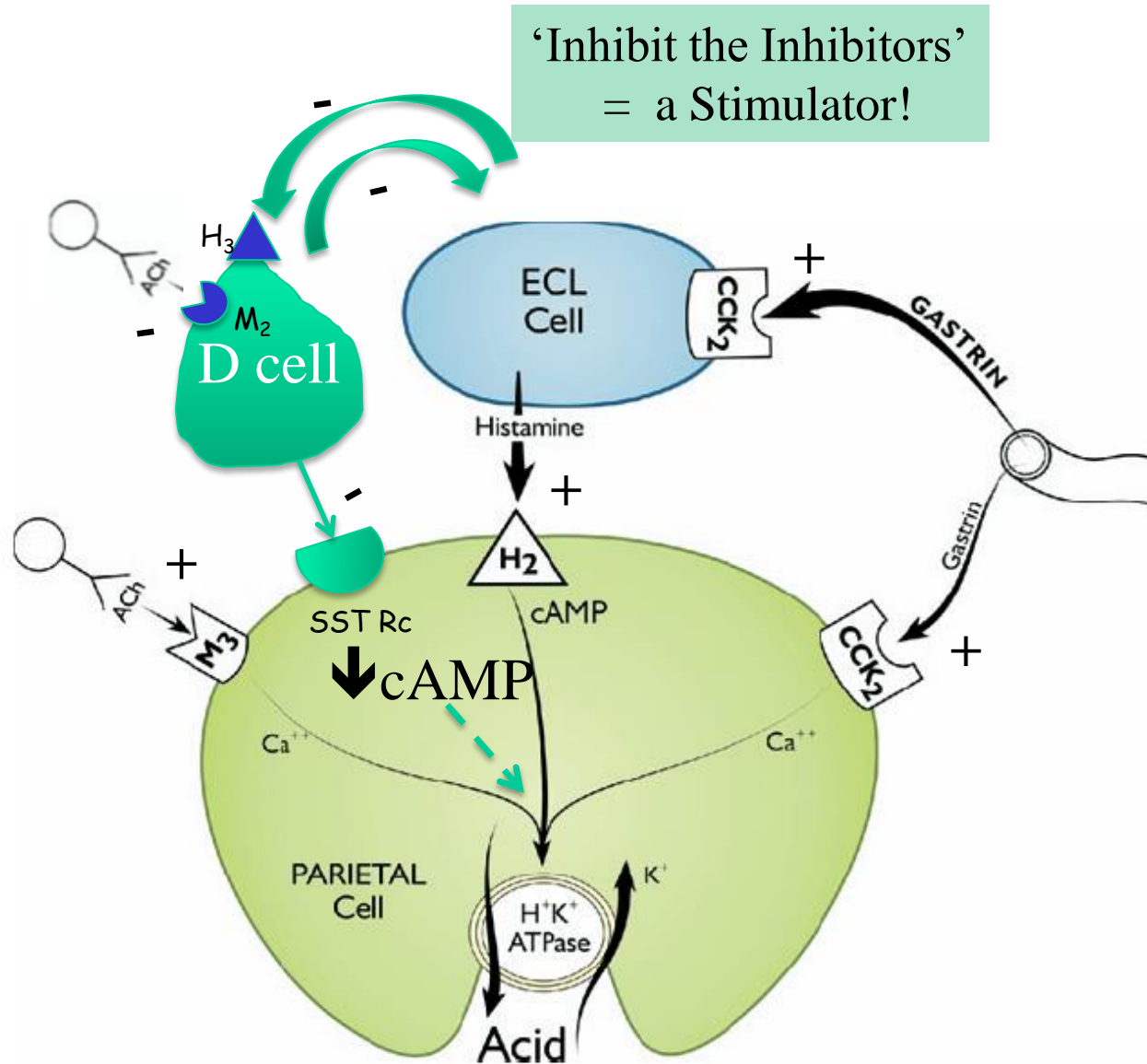
Neural Control of Acid Secretion

- Mucosal nerves respond to cephalic phase and to gastric distention and presence of AA.
 - Bombesin (Gastrin Releasing Peptide)
 - Increases Gastrin production
 - Vasoactive intestinal peptide (VIP)
 - Increased acid secretion due to ECL stimulation (transient)
 - Decrease acid secretion via enhanced somatostatin release (sustained)
 - Pituitary adenylate cyclase-activating polypeptide (PACAP)
 - Stimulated EC cells to release ANP
 - Increased histamine release

Neural Control of Acid Secretion

- Acetylcholine release
 - Increase acid secretion
 - Stimulates Gastrin secretion
 - Released from postganglionic nerves in Meissner's plexus
 - Binds to M3 muscarinic receptors on parietal cells
 - » Increase intracellular calcium
 - » Activate proton pump
 - Inhibits somatostatin secretion by activation of M2 and M4 receptors on D cells
 - Stimulates histamine release from ECLs by binding to to M1 receptor.

Summary of Parietal Cell Control



Prostaglandins

- Inhibit acid secretion
 - Receptors on parietal cells and gastric mucous cells
 - Decrease histamine-stimulated parietal cell function
 - Decrease gastrin stimulated histamine release
- Prostaglandins are product of macrophages and capillary endothelial cells
- Stimulate bicarbonate secretion

Other Regulators

- Transforming growth factor-alpha (TGF-alpha) in parietal cells
 - Inhibits gastric acid secretion
- Peptide YY
 - Released from ileum and colons cells post-prandially
 - Inhibits gastric phase of acid secretion
 - Binds to ECL cells, inhibiting gastrin stimulated histamine release

Inhibition of Acid Secretion

- Carbohydrates in intestine decrease acid secretion – mechanism?
- Fat inhibits acid secretion
 - CCK release
 - Neural response activation

Gastrointestinal Hormones and Peptides

- Leptin (Hormone)
 - Produced by adipose tissue
 - Present in fundic glands
 - Pepsinogen granules of chief cells
 - Inhibitory granules of endocrine-type cells
 - Mobilized following food ingestion after a fast
 - Role in satiety
- Ghrelin (Hormone)
 - Increased secretion with fasting and inhibited by eating
 - In gastric mucosal endocrine cells
 - Stimulates gastric motility and gastric acid secretion
 - Increase gastric emptying
 - Also stimulates growth hormone and insulin secretion

Gastrointestinal Secretions

- Orexin
 - Increases food intake
 - Bind and activate 2 G protein-coupled receptors
 - Peripheral stimulation of gastric acid secretion

Gastrointestinal Secretions

- Adrenomedullin (Peptide)
 - Localized in ECLs in gastric fundus
 - Stimulates gastric Somatostatin via neural pathways
 - Inhibits histamine and gastric acid secretion
 - Expression increases with gastric mucosal injury

Enterogastrones

- Factors that inhibit acid secretion following arrival of nutrients in the intestine.

Include:

- CCK
- Secretin
- Neurotensin
- GLP-1
- Glicentin
- Oxyntomodulin

Gastrointestinal Secretions

- Cholecystokinin (CCK)
 - Decreases acid secretion
 - Binding to CCKa receptors on gastric mucosal somatostatin cells
 - Dominates secretory function
 - Stimulates acid secretion
 - Binding to CCKb receptors on parietal and ECL cells

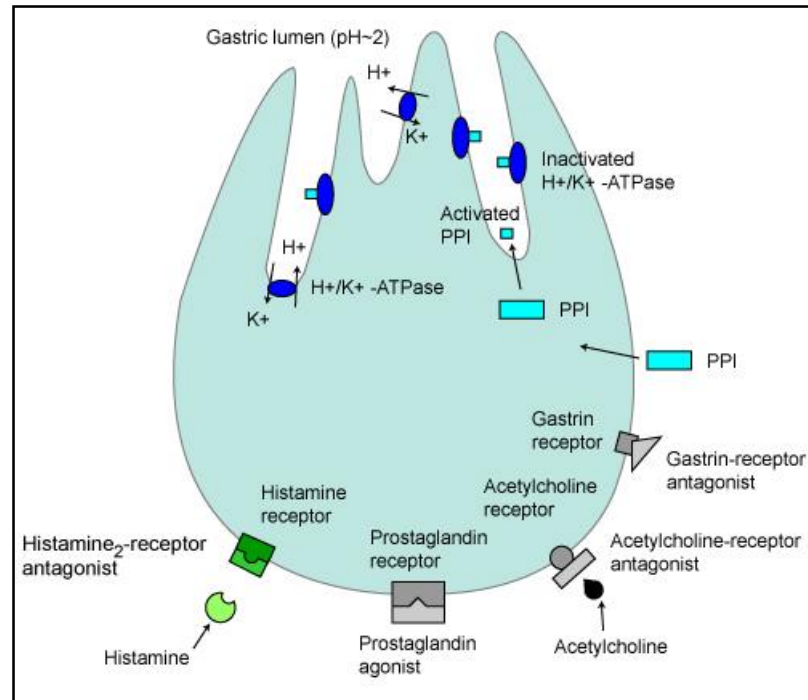
Gastrointestinal Secretions

- Secretin
 - Inhibits gastrin release
 - Decrease gastric acid secretion
 - Secretin containing cells mainly in small intestine
 - Duodenal cells release secretin in response to detection of gastric acid in small intestine lumen
 - Also released when bile salts and products of fat and protein digestion enter the small intestine
 - Stimulates pancreatic exocrine secretion of water and bicarbonate

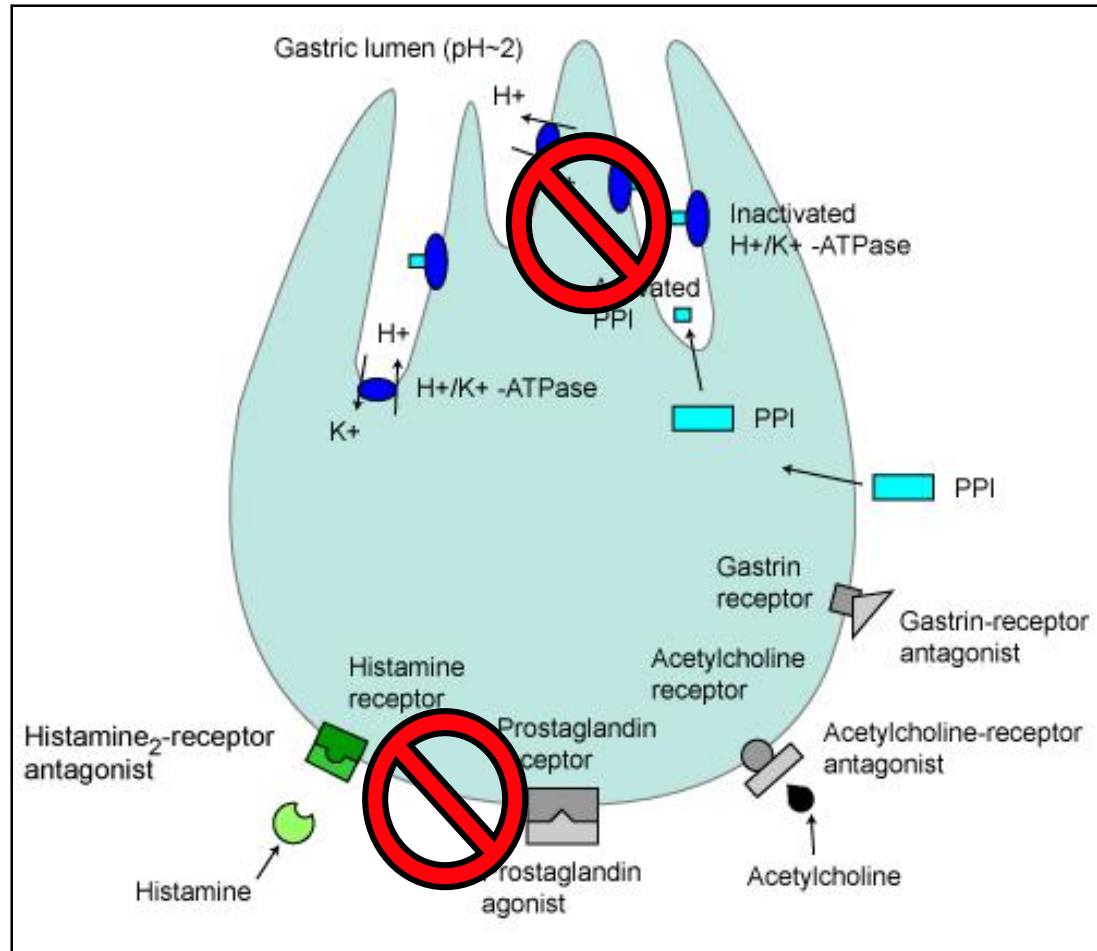
Enterogastrones Mechanisms

- Neurotensin – released by cells in the ileum in response to intraluminal fat
- GLP-1, glicentin and oxyntomodulin are co-localized in L cells.
 - L cells increase in density in the small intestine.
 - Released due to presence of luminal lipids and carbohydrates.
 - Excess secretion of GLP-1 contributes to hypoglycemia in patients with accelerated gastric emptying.

Acid Blocking Medicine



Acid Blocking Medicine



Acid Blocking Medicine

Clinical Correlation

- Proton Pump Inhibitors
 - Increased number of parietal cells
 - Reduction of somatostatin levels
 - Increased Gastrin.
 - Hypergastrinemia induces ECL and parietal cell hyperplasia.

Acid Blocking Medicine

Clinical Correlation

- H2RA tolerance develops
- Patients on prolonged H2RA or PPI will have a rebound of acid secretion due to cellular hyperplasia from PPI use.
- Excess acid secretion reduces in 4-6 weeks.

Evaluation of Gastric Acid Secretion

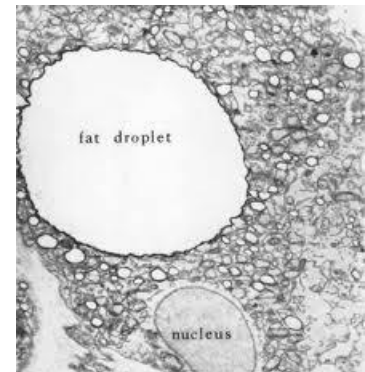
- NG sampling of gastric fluid (Gold Standard)
- pH Probe
- SmartPill
- ^{13}C -labeled calcium carbonate breath test

Gastric Mucus and Bicarbonate

- Mucus
 - Highly hydrated gel (95% H₂O, 5% mucin and electrolytes)
 - Mucus cells on luminal surface and down into the glands
 - Protects epithelium
 - Prostaglandins and secretin stimulate secretion of Bicarbonate

Gastric Enzymes

- Gastric Lipase
 - Initiates digestion of fats
 - Hydrolyzes 20% of triglycerides
 - Resistant to acid
 - Secreted by fundic chief cells
 - Detectable by 10 weeks of gestation



Gastric Enzymes

- Pepsinogen
 - Secreted by gastric chief cells
 - Proenzyme converted to pepsin by gastric acid
 - Necessary for protein digestion
 - Stimulated by cephalic vagal input
 - Secretion enhanced by:
 - ACh
 - CCK and gastrin
 - Decreased secretions associated with anticholinergics, H2RAs, and vagotomy
 - Present by 32-36 gestation

Pepsin

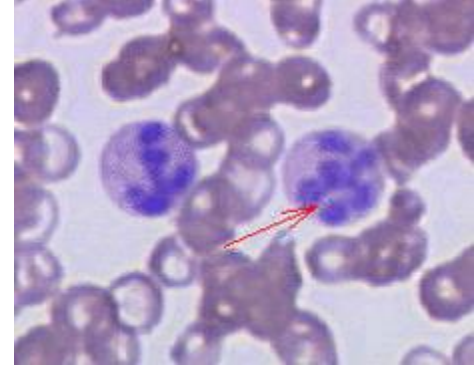
- Digestive enzyme necessary for protein digestion
- Mucolytic
- Ulcerogenic

- Pepsin can autocatalyze pepsinogen to pepsin
- Pepsin inactive at pH >4

Gastric Peptides

- Intrinsic Factor (IF)
 - Parietal (body and fundus) cells secrete
 - Binds Vitamin B₁₂
 - 1-5µg B₁₂ absorbed daily (3-30µg in diet)
- Intrinsic Factor – Vitamin B₁₂ complex
 - Binds to Cubilin receptor in the ileal mucosa
 - Absorbed by endocytosis
 - In enterocytes,
 - Cyanocobalamin transferred from IF to transcobalamin II
 - Transports cyanocobalamin to plasma
 - Cobalamin converted to active forms
 - Methylcobalamin and 5-deoxyadenyosyl cobalamin

Case #2



- 17 yo female with diabetes presents with several months of fatigue, recurrent candidiasis and worsening migraines
- Her evaluation has identified
 - Megaloblastic anemia
 - Negative screens for thyroid and celiac disease

Case #2

- Physical exam
 - HR 110 bpm RR 30
 - Pale
 - Abdomen is soft with positive bowel sounds and she is non-tender with no masses
- EGD
 - Thin rugae with no visible inflammation
 - Biopsy with severe atrophic fundic gland gastritis.
 - No visible parietal cells

Atrophic Gastritis

- Present in 2% of the population and 10% of patients with type I diabetes.
- Autoantibodies to parietal cells
- Achlorhydria due to absence of parietal cells
- Megaloblastic anemia due to vitamin B₁₂ deficiency associated with loss of intrinsic factor

Questions

- A 17 yo Mexican immigrant child has worsening abdominal pain over several months and develops black, tarry stools. She is seen and evaluated in the emergency department. A smart GI fellow is concerned about an acute *H. Pylori* infection. What is the most cost-effective test to confirm the diagnosis?
 - Upper Endoscopy with Biopsy for Histology
 - Upper Endoscopy with Biopsy for rapid urease test
 - Serum *H. Pylori* IgG
 - Stool *H. Pylori* antigen
 - Urea Breath test

Review Question

- A patient has been taking a PPI for years and would like to stop therapy due to cost. You recommend they slowly wean off therapy to minimize what problem?
 - Elevated serum histamine
 - Acid hyper-secretion
 - Development of gastritis
 - Low serum gastrin
 - Hypoglycemia
- What substance is most important to acid release?
 - Histamine
 - Gastrin
 - Somatostatin
 - CCK

Questions



Please send any questions or comments to

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