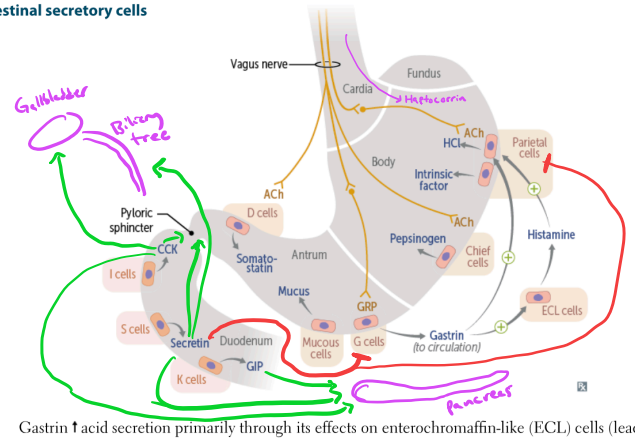
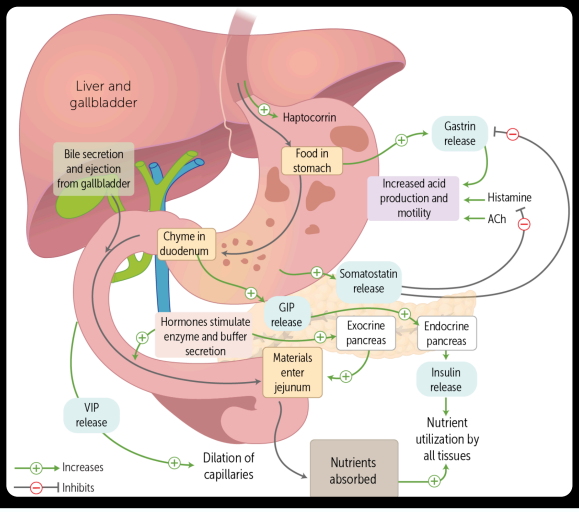
GI Regulation & Secretion Overview

Locations of gastrointestinal secretory cells



Gastrin ↑ acid secretion primarily through its effects on enterochromaffin-like (ECL) cells (leading to histamine release) rather than through its direct effect on parietal cells.

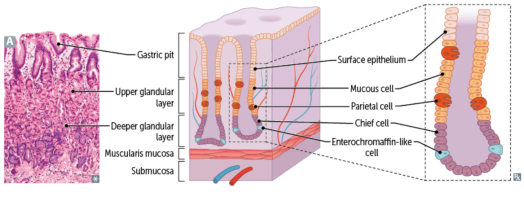


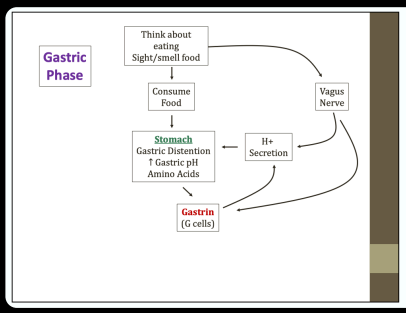
Gastrointestinal regulatory substances

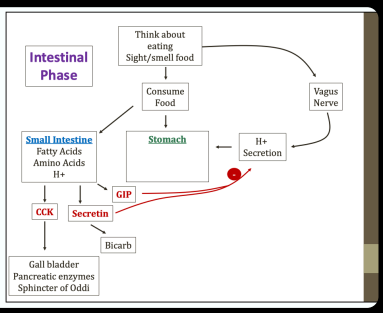
REGULATORY SUBSTANCE	SOURCE	ACTION	REGULATION	NOTES
Gastrin	G cells (antrum of stomach, duodenum)	↑ gastric H^+ secretion ↑ growth of gastric mucosa ↑ gastric motility	↑ by stomach distention/ alkalinization, amino acids, peptides, vagal stimulation via gastrin-releasing peptide (GRP) ↓ by pH < 1.5	↑ by chronic PPI use ↑ in chronic atrophic gastritis (eg, *H pylori*) ↑↑ in Zollinger-Ellison syndrome (gastrinoma)
Somatostatin	D cells (pancreatic islets, GI mucosa)	↓ gastric acid and pepsinogen secretion ↓ pancreatic and small intestine fluid secretion ↓ gallbladder contraction ↓ insulin and glucagon release	↑ by acid ↓ by vagal stimulation	Inhibits secretion of various hormones (encourages somato-stasis) Octreotide is an analog used to treat acromegaly, carcinoid syndrome, and variceal bleeding
Cholecystokinin	I cells (duodenum, jejunum)	↑ pancreatic secretion ↑ gallbladder contraction ↓ gastric emptying ↑ sphincter of Oddi relaxation	↑ by fatty acids, amino acids	Acts on neural muscarinic pathways to cause pancreatic secretion
Secretin	S cells (duodenum)	↑ pancreatic HCO_3^- secretion ↓ gastric acid secretion ↑ bile secretion	↑ by acid, fatty acids in lumen of duodenum	↑ HCO_3^- neutralizes gastric acid in duodenum, allowing pancreatic enzymes to function
Glucose-dependent insulinotropic peptide	K cells (duodenum, jejunum)	Exocrine: ↓ gastric H^+ secretion Endocrine: ↑ insulin release	↑ by fatty acids, amino acids, oral glucose	Also called gastric inhibitory peptide (GIP) Oral glucose load ↑ insulin compared to IV equivalent due to GIP secretion
Motilin	Small intestine	Produces migrating motor complexes (MMCs)	↑ in fasting state	Motilin receptor agonists (eg, erythromycin) are used to stimulate intestinal peristalsis.
Vasoactive intestinal polypeptide	Parasympathetic ganglia in sphincters, gallbladder, small intestine	↑ intestinal water and electrolyte secretion ↑ relaxation of intestinal smooth muscle and sphincters	↑ by distention and vagal stimulation ↓ by adrenergic input	VIPoma—non-α, non-β islet cell pancreatic tumor that secretes VIP; associated with Watery Diarrhea, Hypokalemia, Achlorhydria (WDHA syndrome)
Nitric oxide		↑ smooth muscle relaxation, including lower esophageal sphincter (LES)		Loss of NO secretion is implicated in ↑ LES tone of achalasia
Ghrelin	Stomach	↑ appetite ("ghrowlin' stomach")	↑ in fasting state ↓ by food	↑ in Prader-Willi syndrome ↓ after gastric bypass surgery

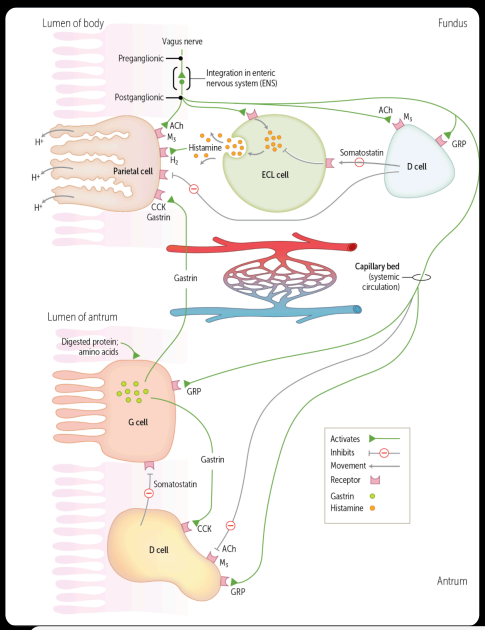
Gastrointestinal secretory products

PRODUCT	SOURCE	ACTION	REGULATION	NOTES
Intrinsic factor	Parietal cells (stomach A)	Vitamin B_{12}–binding protein (required for B_{12} uptake in terminal ileum)		Autoimmune destruction of parietal cells → chronic gastritis and pernicious anemia.
Gastric acid	Parietal cells (stomach)	↓ stomach pH	↑ by histamine, vagal stimulation (ACh), gastrin ↓ by somatostatin, GIP, prostaglandin, secretin	
Pepsin	Chief cells (stomach)	Protein digestion	↑ by vagal stimulation (ACh), local acid	Pepsinogen (inactive) is converted to pepsin (active) in the presence of H^+.
Bicarbonate	Mucosal cells (stomach, duodenum, salivary glands, pancreas) and Brunner glands (duodenum)	Neutralizes acid	↑ by pancreatic and biliary secretion with secretin	Trapped in mucus that covers the gastric epithelium.









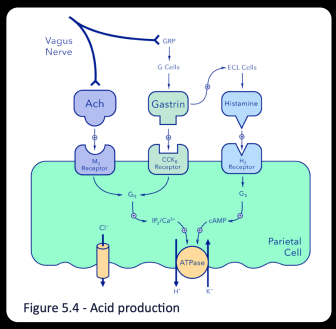


Figure 5.4 - Acid production

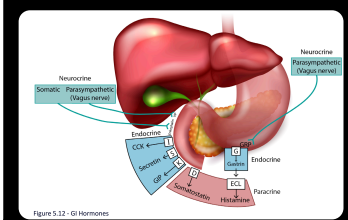


Figure 5.12 - GI Hormones

GI Secretion	Approximate Volume (mL)	Major Characteristics	Substances Present
Saliva	1500	↑ HCO_3^- ↑ K^+ Hypotonic to plasma	Amylase Lysozyme Lactoferrin Peroxidase Haptocorrin Lingual lipase
Stomach	2500	↑ HCl	Intrinsic factor Pepsinogen
Small intestines	1000	↑ HCO_3^-	Enterokinase (enteropeptidase) GIP GLP-1
Pancreas	1500	↑ HCO_3^-	Trypsinogen Amylase Lipase Peptidases

Mnemonic for hormones released by ↑ fat:

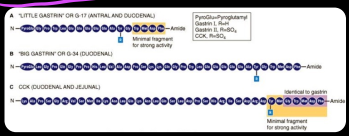
Fat or SIK:

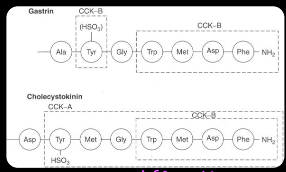
↑ Fat → S cells → secretin
I cells → CCK
K cells → GIP

} Combine effects summary:
① Breakdown Fat (pancreatic enzymes)
② Absorb glucose (↑ pancreatic β-cells)
③ ↑ pH (↓ H^+ secretion)

Primary Hormones

Gastrin & CCK Homology





* Difference in last 4-7 AAs on C terminus → functional difference
  - CCK-A receptors - bind strongly to last 7 AAs on CCK
    - ↳ ↑Km for Gastrin b/c only has the 4 AA sequence @ C-term.
  - CCK-B receptors - ↓Km for only the specific 4 AA sequence
    - ↳ strongly binds BOTH Gastrin & CCK w/equal affinity
  - ↳ BOTH CCK-A & CCK-B receptors → ↑$G_{\alpha q}$ → ↑PLC →(PIP_2)→ DAG + IP_3
    - → DAG → ↑PKC
    - → IP_3 →(ER)→ ↑Ca^{2+} release

Gastrin

- Secreted through basal face of G cells in glands of mucosa
  1. stomach antrum
  2. Duodenum

  } secreted into portal vein blood
- G cells stimulated by:
  - Chemical detection → ↑[peptides/AAs], [Ca^{2+}], & [H^+] in lumen
  - Mechanical detection → stomach distension from food entering → stretch → Vagus nerve → GRP (bombesin) released → activates G cells
  - "Thinking about food" → Vagus nerve → post-ganglionic cells in enteric nervous system (ENS)
    - ↳ release gastrin-releasing peptide (GRP) → GRP binds G-cells → gastrin release
  - Vagus nerve ALSO inhibits D cells via GRP & ACh on M_3 receptors
    - → ↓somatostatin → G cell disinhibition
    - Somatostatin inhibits G cells via binding $G_{\alpha i}$-coupled receptors on both ECL cells & G cells
- G cells inhibited by somatostatin, Secretin, ↑[H^+] (pH<1.5, feedback inhibition)
- Gastrin → ↑[H^+] release via:
  1. Binding enterochromaffin-like cells (ECL) → histamine release → histamine binds H_2 receptors on parietal cells → ↑$G_{\alpha s}$ → ↑AC → ↑cAMP → ↑PKA → ↑H^+/K^+ ATPase antiporter
     * This is most important/primary mechanism by which Gastrin → ↑[H^+], via ECL stimulation, NOT by direct parietal cell stimulation BECAUSE of PROXIMITY effects
       - ↳ ECLs most effectively communicate w/ parietal cells b/c located within gastric glands w/ parietal cells. G cells located further away in antrum
  2. Binding parietal cells directly on Cholecystokinin B (CCK-B) Gq-coupled receptors → ↑$G_{\alpha q}$ → ↑GC → ↑cGMP → ↑PLC
     - → PIP_2 converted to IP_3 → ER → ↑Ca^{2+} release → ↑Ca^{2+}
     - → ↑H^+/K^+ ATPase antiporter
- ↑ mucosal proliferation in epithelial lining of stomach
- ↑gastric motility → ↑ mechanical digestion
- Constricts pyloric sphincter
  - ↳ traps food inside stomach for adequate breakdown
- Gastrinoma - Zollinger Ellison Syndrome - Gastrin-secreting tumor in duodenum or pancreas
  - (fetus has pancreatic G cells that can (rarely) persist into adulthood → gastrinoma)
  - ↳ ↑↑[H^+] secretion
  - ↳ ↑↑ hypertrophy/hyperplasia of mucosa
  - Abdominal Pain (due to ↑H^+, improves w/ food)
  - Chronic diarrhea due to ↑↑[H^+] → too much to be fully neutralized in intestine
    - ↳ activates pancreatic enzymes
    - Inhibits Na^+ & H_2O reabsorption in intestines
  - Ulcers - Mostly in distal duodenum or jejunum, refractory to PPI Tx
  - Heartburn
  - * Dx → secretin test: Gastrinomas stimulated by secretin (normal G cells inhibited) → will see ↑gastrin
  - * Tx: PPIs (omeprazole, lansoprazole), octreotide, surgery

Cholecystokinin (CCK)

- released by I-cells in duodenum & jejunum (Small Intestine)
  - "Iron-Chef cells" → "prepare food" coming into intestinal epithelium
- release stimulated by Fatty Acids & Amino Acids (proteins)
  - ↳ FAs & proteins = hard to digest macromolecules → require assistance by CCK
- Bolus of food enters duodenum → stretch → CCK-releasing peptide released → binds receptors on I-cells → stimulates CCK secretion into blood → binds CCK receptors on vagus nerve → ACh ⇒:
  - → pancreas exocrine CCK-1 receptors → release HCO_3^- & digestive enzymes
  - → gallbladder → contraction → bile release
  - → Sphincter of Oddi → relaxation → bile/pancreatic juices enter duodenum
  - → pyloric sphincter → contraction → ↓ gastric juices into duodenum
- → ↓ gastric motility → ↑ satiety

Somatostatin

- released by:
  - D cells - GI mucosa (antrum)
  - δ cells - endocrine pancreas (islets of langerhans)
- D cells stimulated by ↓pH (↑[H^+]) & ↑[pepsinogen] in GI lumen (basically, stimulated when chyme present)
- D cells inhibited by vagus nerve via ACh → M_3 receptors
  - ↳ allows digestion to continue
- Major function = down regulation of GI activity via $G_{\alpha i}$ receptors
  - Stomach:
    - inhibits G cells
    - inhibits ECL cells

    } → ↓[H^+] secretion
  - Small intestine:
    - ↓ intestinal fluid secretion by inhibiting S cells (secretin release) AND VIP release } ↓HCO_3^- secretion
    - Inhibits I-cell enzymatic secretions (CCK)
    - * No effect on K cells (GIP)
    - Inhibits Motilin & VIP release → ↓fluid & ↓peristalsis
  - Gallbladder:
    - Inhibits CCK release → ↓ gallbladder contraction
  - Pancreas:
    - inhibits pancreatic islet α (glucagon) & β (insulin) cells & exocrine cells → ↓enzyme & HCO_3^- release

* Somatostatin also found in nerves → inhibits growth hormone release by binding hypothalamus

- Octreotide - Synthetic somatostatin analogue used to control many GI endocrine symptoms
  - Reduces splanchnic blood flow in bleeding varices
  - Carcinoid Syndrome
    - improves flushing & diarrhea
  - Acromegaly
    - inhibits growth hormone secretion
  - Gastrinoma/Glucagonoma
    - inhibits hormone release

Secretin Family

- Secretin, glucagon, VIP, GIP

Peptide	# of amino acids	# residues = secretin
secretin	27	27
glucagon	29	14
GIP	42	9*
VIP	28	9

* 15 of first 26 are identical to glucagon

* All activate $G_{\alpha s}$ → cAMP → PKA

Secretin

- release stimulated by ↓pH (from ↑[H^+]) & ↑[Free FAs] & ↑[Glucose]
- released by S cells in duodenal epithelium into blood
- binds smooth muscle in pyloric sphincter → Contraction
  - ↳ ↓chyme entering duodenum until present acid neutralized
- binds pancreatic receptors
  - ↳ pancreas exocrine → ↑Cl^-/HCO_3^- antiporter → ↑ HCO_3^- release → ↑pH
  - Pancreas endocrine → Somatostatin release
    - ↳ Somatostatin binds receptors on G cells & parietal cells
      - ↳ inhibits Gastrin & H^+ release, respectively
- binds biliary receptors → exocrine HCO_3^- release
- inhibits parietal cells → inhibits H^+ release

Vasoactive Intestinal Polypeptide (VIP)

- released by ENS PSNS ganglia
- Stimulated by:
  - intestinal wall distention (from entering food)
  - Vagus nerve (PSNS)
- inhibited by catecholamines (e.g. epinephrine)
- relaxes smooth muscle in intestine AND following sphincters (esophageal, pyloric, gallbladder, Oddi)
  - ↳ also causes vasodilation in intestinal capillaries
- Stimulates pancreatic HCO_3^- secretion → ↑pH
  - ↳ H_2O follows HCO_3^- → ↑ H_2O secretion
- Inhibits Gastric H^+ secretion
- Stimulates H_2O & electrolyte secretion into intestinal lumen
- Stimulates motility & secretions
  - ↳ couples w/ ENS reflex arc to regulate motility & secretions throughout GI tract
- VIPoma - pancreatic tumor → ↑↑↑ VIP secretion → WDHA Syndrome
  - Watery Diarrhea, Hypokalemia, Achlorhydria
  - Tx: Fluid/electrolyte replacement, octreotide

Glucose-dependent Insulinotropic Enzyme (GIP)

- aka gastric inhibitory peptide
- Secreted by K cells in duodenum & jejunum
  - release stimulated primarily by glucose (orally ingested) * and also by FAs & AAs
- Function: Incretin
  - Endocrine
    - activates $G_{\alpha s}$-coupled receptor in pancreatic β-cells → ↑insulin packaged in secretory granules for eventual release
      - ↳ for this reason, cells able to utilize oral glucose load more rapidly than equivalent IV-administered glucose load
  - Exocrine
    - inhibits parietal cells → ↓[H^+] secretion
    - slows gastric emptying

Secretory Hormones

Bombesin (GRP)
- aka gastrin-releasing peptide (GRP)
- multifunctional neuropeptide
- stimulated AND released by Vagus nerve
- Paracrine - stimulates nearby G cells → ↑ Gastrin release
- Neuromodulator - negative feedback to brain to signal to stop eating ⇒ satiety hormone
  - works in conjunction w/ CCK

Glucagon-like Peptide 1 (GLP-1)
- secreted by:
  - L-cells in intestinal epithelium (duodenum, jejunum, ileum, colon)
  - Nucleus Tractus Solitarius (NTS) neurons
- stimulated by orally-ingested glucose
- GLP-1 = incretin
  1. enhances & prolongs effects of insulin
     - bind G_{as} coupled receptors in pancreatic β-cells → ↑ cAMP → ↑ PKA → ↑ insulin packaging (e.g. insulin priming for greater granular load when released
     - ↳ Liraglutide = injectable form of GLP-1 used to control blood sugar in type II diabetics
     - ↳ anorexigenic effect
  2. Inhibits $[H^+]$ secretion & slows gastric emptying

Glucagon-like Peptide-2 (GLP-2)
- secreted by:
  - CNS neurons
  - L-cells (intestinal epithelium)
- many functions:
  - ↑ mucosal growth
  - ↑ villi surface area → ↑ absorption
  - protects neurons of myenteric plexus

Peptide YY (PYY)
- PYY = Peptide w/ 2 Tyr residues
- Secreted by:
  - L-cells in intestinal epithelium
- Stimulated by fat in lumen
- binds neuropeptide Y (NPY) receptor
  - ↑ colonic H_2O & NaCl reabsorption
  - ↓ gastric secretion
  - ↓ gastric emptying
  - ↓ pancreatic enzyme secretion
  - binds arcuate nucleus in hypothalamus
    - ↳ anorexigenic (↑ satiety, ↓ hunger)

Oxyntomodulin
- Secreted by intestinal cells
- stimulated by food intake
- = ↓ appetite & food consumption AFTER food intake

Ghrelin
- secreted by Parietal glands in fundus of stomach during fasting
  - inhibited by stomach stretch receptors → indicating stomach is full
    - ↳ stomach not full → ↓ stretch → disinhibits parietal glands → ↑ Ghrelin release
- Stimulates lateral hypothalamic nucleus → pituitary → ↑ GH, ↑ ACTH (→ ↑ cortisol), ↑ prolactin
- ↳ orexigenic (↑ hunger)
- ↑ gastric emptying
- ↑ gastric motility
- ↑ $[H^+]$ secretion
- ↑ insulin sensitivity
- ↓ insulin secretion
- monitors adipose storage: ↑ adipose → ↓ [ghrelin]
  - ↳ obesity → ↑↑↑ [adipose] → ↓ [ghrelin]
- sleep deprivation → ↑ [ghrelin] → obesity
- Prader-Willi Syndrome → ↑↑ [ghrelin] → Morbid obesity
- Gastric Bypass Surgery → Parietal gland bypassed → ↓ [ghrelin]

Leptin
- Synthesized & secreted by adipose based on [fat] stored in adipocytes
  - ↳ ↑ fat → ↑ Leptin secretion
- Can circulate freely OR bound to leptin-binding protein (Leptin-BP)
  - bound form (Leptin-BP) has greater effect bc can only cross BBB when bound to Leptin-BP
  - ↳ targets arcuate nucleus (ventromedial hypothalamic nucleus) → ↓ appetite, ↑ energy expenditure
    - ↳ anorexigenic
    - ↳ ↓ Leptin → hyperphagia (abnormally ↑ appetite for food)
    - ↳ Dieting → ↓ Leptin → ↑ appetite but ↓ energy expenditure
      - ↳ want to eat more & store more energy → not good for trying to exercise
- Inhibits neuronal hormones that ↑ appetite
  - e.g. neuropeptide Y
- Obesity → ↓ leptin sensitivity due to ↓ [Leptin-BP] & ↓ leptin receptors in brain
  - ↳ ↓ sensitivity = takes more hormone to achieve same satiety effect
    - ↳ pt. continues to eat & eat w/o feeling full
- Underweight → ↑ leptin sensitivity → ingesting a little bit of food will quickly achieve satiety trigger → won't consume as much food as they should

Motilin
- Secreted by M cells in small intestine (upper duodenum)
  - stimulated by TPN (↑ $[OH^-]$) due to fasting (→ ↓ $[H^+]$ secretion)

*Motilin only stimulates MMC in absence of food
  - ↳ when food is present, motilin secreted for baseline intestinal peristalsis
- stimulates migrating motor complex (MMC) during fasting
  - ↳ produces long, slow peristaltic waves of contraction in smooth muscle
    - ↳ purpose = clear out intestines to make room for next meal
  - causes Borborygmi → growling/rumbling sounds made by stomach as gas moves through intestines
- food Poisoning/hazardous ingestion → ↑↑↑ motilin secretion → peristalsis "flush" of intestines to protect from further damage

* Erythromycin → binds motilin receptors
  - ↳ used to treat gastroparesis to ↑ motility → improve abdominal pain

Enkephalins
- released from ENS neurons throughout GI tract
- cause smooth muscle contraction → ↓ fluid flow into intestines
  - ↳ opposite of VIP

* Opiates act on enkephalin receptors → ↓ fluid flow → constipation

Major Paracrine Agents in GI tract

Somatostatin
- Secreted by D cells in gastric antrum
  - stimulated by ↑ $[H^+]$
- targets: G cells → ↓ gastrin release, ↓ acid secretion
  - ECL cells → ↓ histamine release

Histamine
- Secreted by:
  1. Oxyntic Mucosa (ECL cells)
     - stimulated by ACh, gastrin
       - ↳ targets parietal cells
         - ↳ ↑ $[H^+]$ secretion
  2. Intestinal mast cells
     - stimulated by antigens
     - targets mucosal crypt cells
       - ↳ ↑ intestinal $[Cl^-]$ secretion

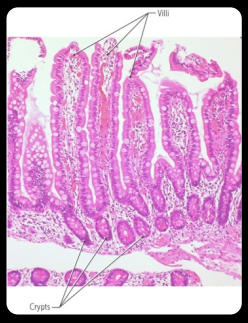
Prostaglandins
- Secreted by Subepithelial Myofibroblasts
- targets:
  - mucosal cells → ↑ intestinal mucus secretion (goblet cells)
  - Blood vessels → vascular regulation
  - parietal cells → ↓ H^+ secretion

Adenosine
- Secreted by various cells
- stimulated by:
  - oxidative stress
    - ↳ targets Mucosa
      - ↳ ↑ intestinal Secretion
  - ↑ cellular activity
    - ↳ targets blood vessels
      - ↳ vascular regulation

Serotonin (5-HT)
- secreted by enterochromaffin cells
- stimulated by specific nutrients in lumen
- targets mucosal cells
  - ↳ regulates secretion & absorption

Hormone Release - Chemical / Mechanical Detection

Chemical Detection



Intestine

- Villi - maintain electrolyte & pH balance
- crypt cells - release hormones & enzymes
- Enteroendocrine cells - located @ base of crypts
  - secrete variety of hormones
  - modified epithelial cells
    - narrow apical side, broad basal side
      ↳ allows ↑↑ secretory granule release from basal side in response to minimal stimulation @ apical side
  - Enterochromaffin cells (EC cells)
    - also Kulchitsky cells
    - located in crypts of intestinal epithelium
    - secrete Serotonin (5-HT) → ↑ myenteric neurons in submucosal plexus → ↑ ACh → gut mucosa releases Cl^- → ↑ peristaltic reflex

- GPCR-coupled
  - different types - each have specific GPCR

- G cells
  - stomach & duodenum
  - highly sensitized to H^+, AAs, & Ca^{2+}
    ↳ gastrin release

- I cells
  - small intestine
  - response to ↑↑ [FAs] & ↑↑ [AAs] in lumen
  - stimulated by binding CCK-releasing peptide to GPCR

- S cells
  - duodenum
  - respond to ↑ FAs, AAs, Glucose
  - secrete secretin

Mechanical Detection

- caused by physical distension of food bolus entering GI tract
  ↳ mechanoreceptors detect ↑ stretch
    ↳ stimulate vagus nerve

↳ Vagus nerve → PSNS ganglia → release:
- ↑ Bombesin (GRP) → G cells → gastrin secretion
- ↑ VIP release → relaxes Pyloric sphincter → food passes into duodenum
  & stretch in stomach → VIP release → food into duodenum →
  duodenal stretch → more VIP released to increase
  fluid & electrolyte secretion

↳ Vagus nerve direct effects:
- stimulates G cells → ↑ gastrin
- inhibits D cells → ↓ somatostatin
  ↳ facilitates ↑ gastrin release
- Stimulates Chief cells → ↑ pepsinogen release

Enteric Nervous System (ENS) & GI integration

ENS

- ENS = "second brain" of GI system b/c can function autonomously from CNS (SNS & PSNS)
  - formed by afferents, interneurons, & efferents

① Afferent nerves detect mechanical & chemical signals along GI tract

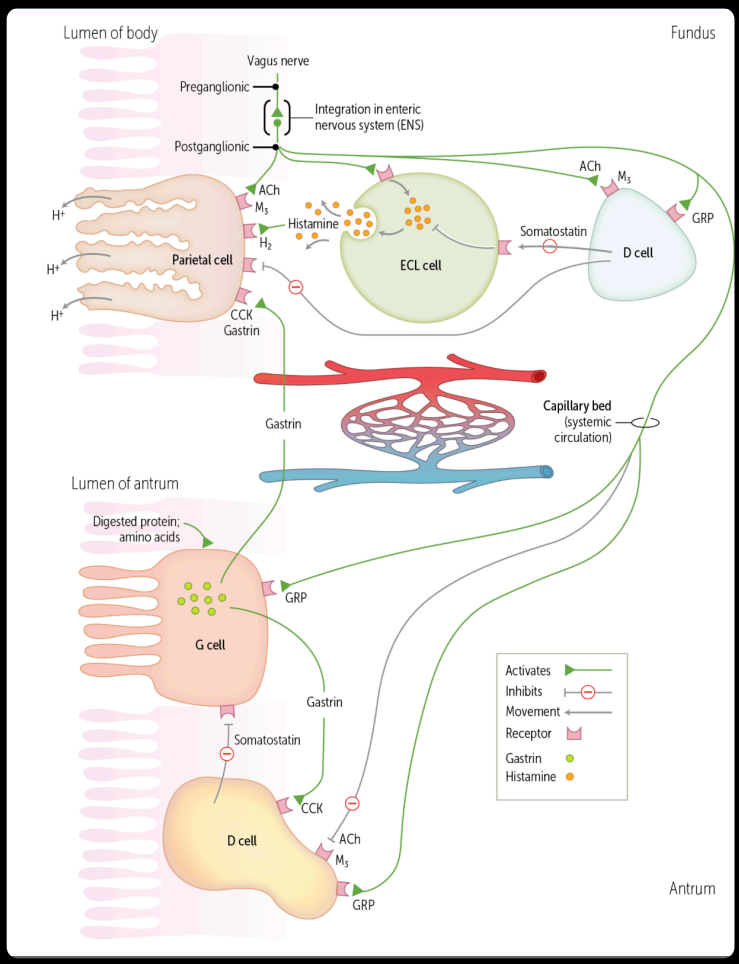
② 2 efferent layers facilitate reabsorption

Submucosal Plexus (Meissner's)
- controls enzyme secretions

Myenteric Plexus (Auerbach's)
- between 2 layers of smooth muscle
  - ↳ controls Peristalsis

- Signaling molecules released by ENS to facilitate digestion:
  - Acetylcholine (ACh)
  - Vasoactive Intestinal Polypeptide (VIP)
  - Dopamine
  - Serotonin (5-HT)
  -

- In Irritable Bowel Syndrome (IBS) - defective 5-HT signaling in ENS → EXCESSIVE OR ABSENT secretion & motility
  - ↳ diarrhea and/or constipation



CNS effects

- PSNS
  - releases ACh → enhances digestion
    - ↳ ↑ [H+] secretion in stomach
    - ↳ ↑ fluid secretion in intestines
    - ↳ smooth muscle contraction in front of bolus
  - releases VIP → enhances digestion
    - ↳ ↑ intestinal fluid release
    - ↳ smooth muscle relaxation behind bolus

- SNS
  - releases catecholamines (Epi/Norepi) → slows digestion
    - ↳ inhibits PSNS input

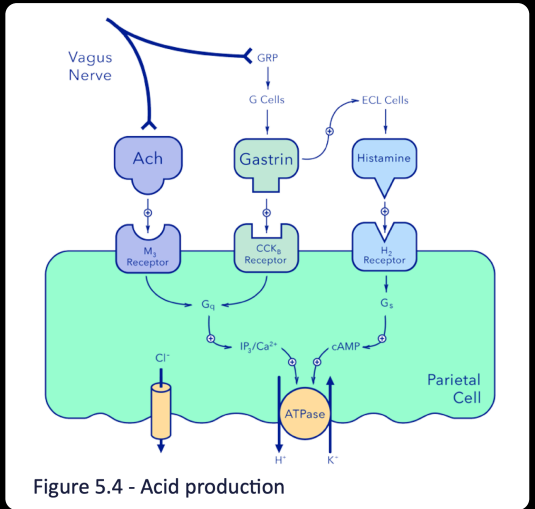


Figure 5.4 - Acid production

Cells w/ neuronal AND hormonal inputs

① G cells - secrete gastrin
- Stimulated by:
  - luminal contents (peptides/AAs, H^+, Ca^{2+})
  - Bombesin (GRP) released by postganglionic PSNS cells BEFORE food enters stomach → anticipating, top down neural effect
  - stretch receptors - once food has arrived in stomach
    - ↳ ↑ gastrin release to:
      - bloodstream
      - nearby nerve plexuses
- Inhibited by somatostatin
  - occurs when stomach pH < 1.5

② Enterochromaffin-like Cells (ECL cells) - secrete histamine
- Stimulated by:
  - gastrin
  - ACh from postganglionic PSNS fibers
- Inhibited by somatostatin

③ Parietal cells - secrete H^+ into stomach lumen
- Stimulated by:
  - gastrin
  - histamine
  - ACh from postganglionic PSNS fibers
- Inhibited by:
  - somatostatin
  - Prostaglandins