Chapter 7

Gastrointestinal Hormones

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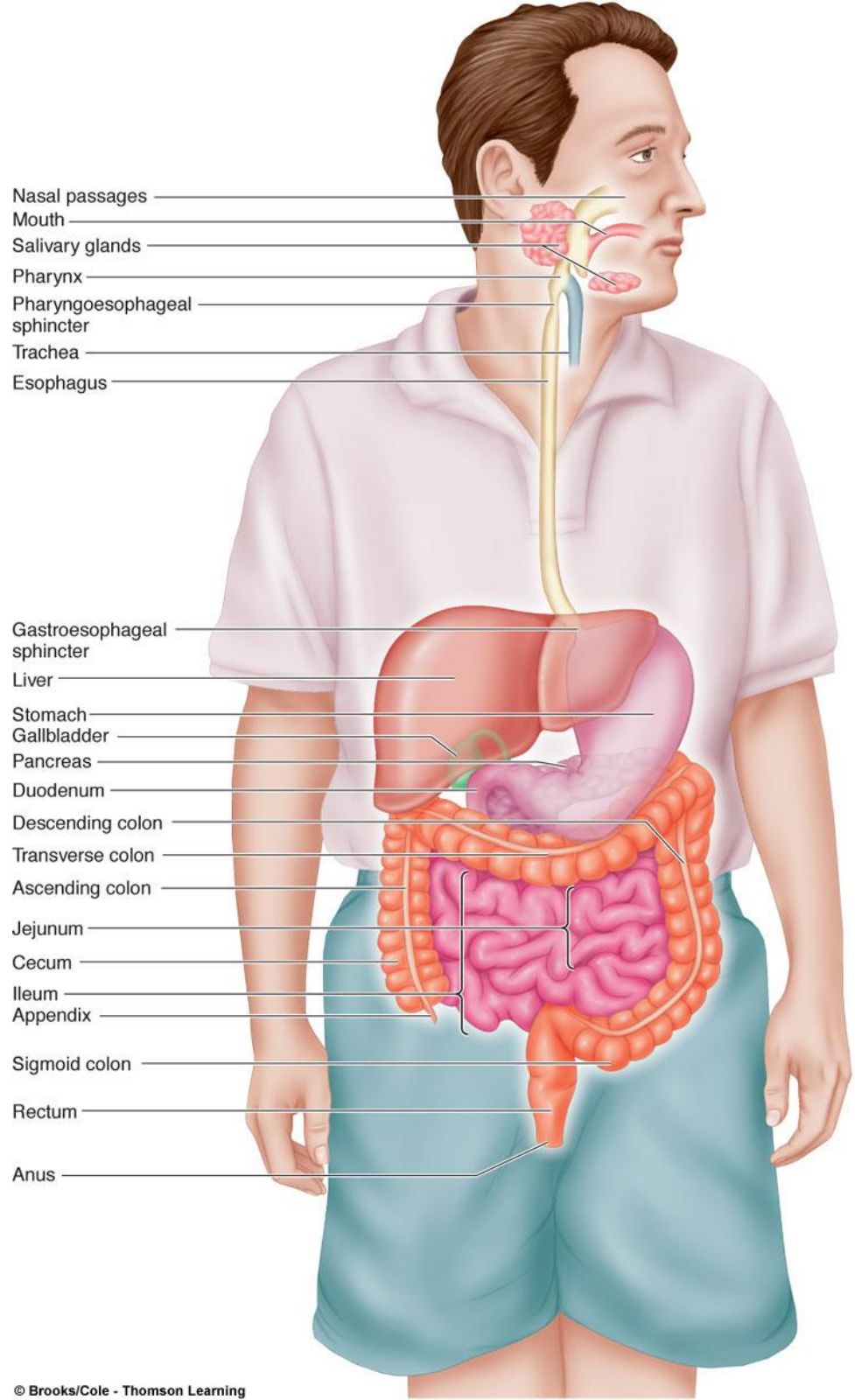
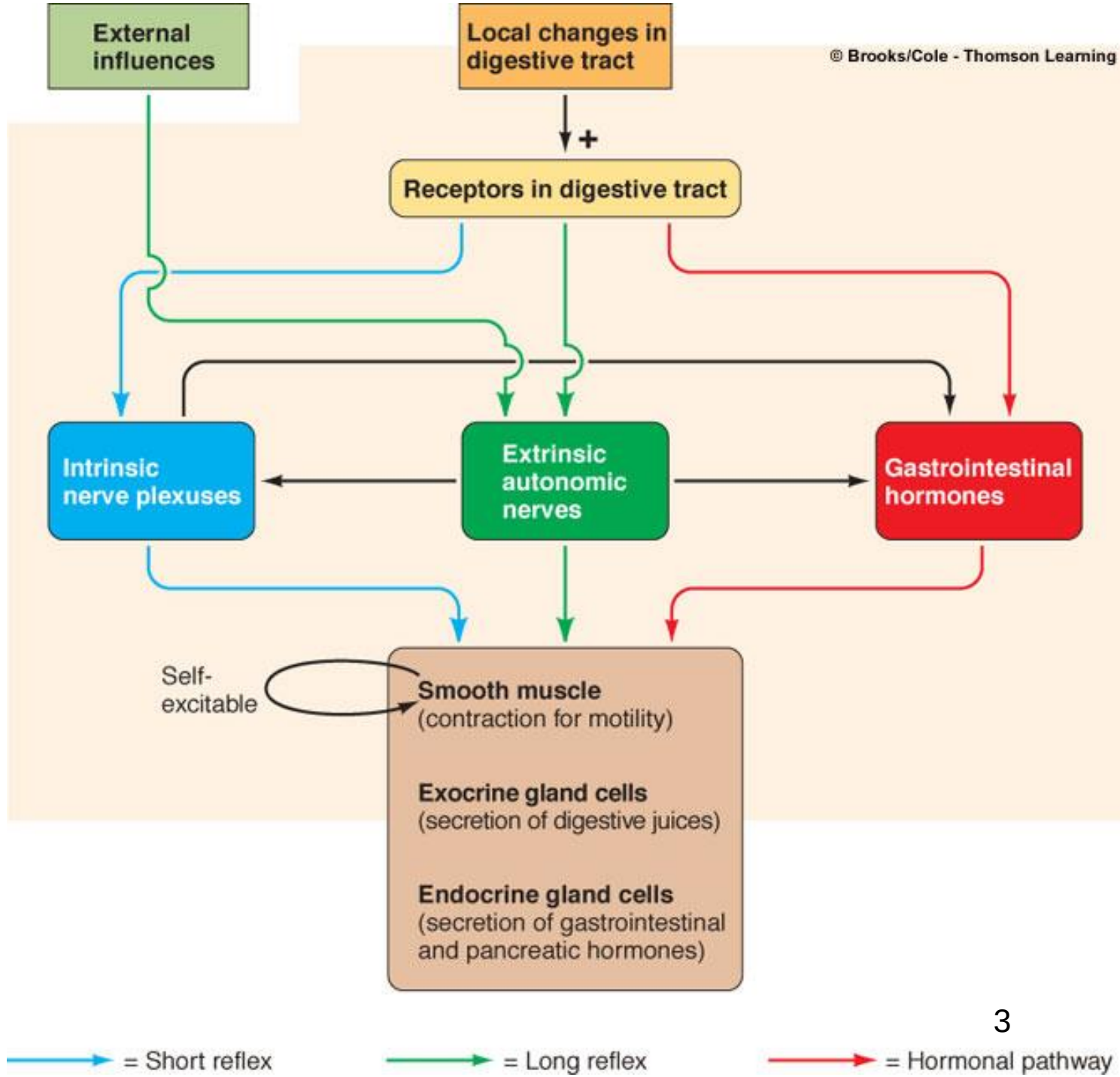
Digestive System

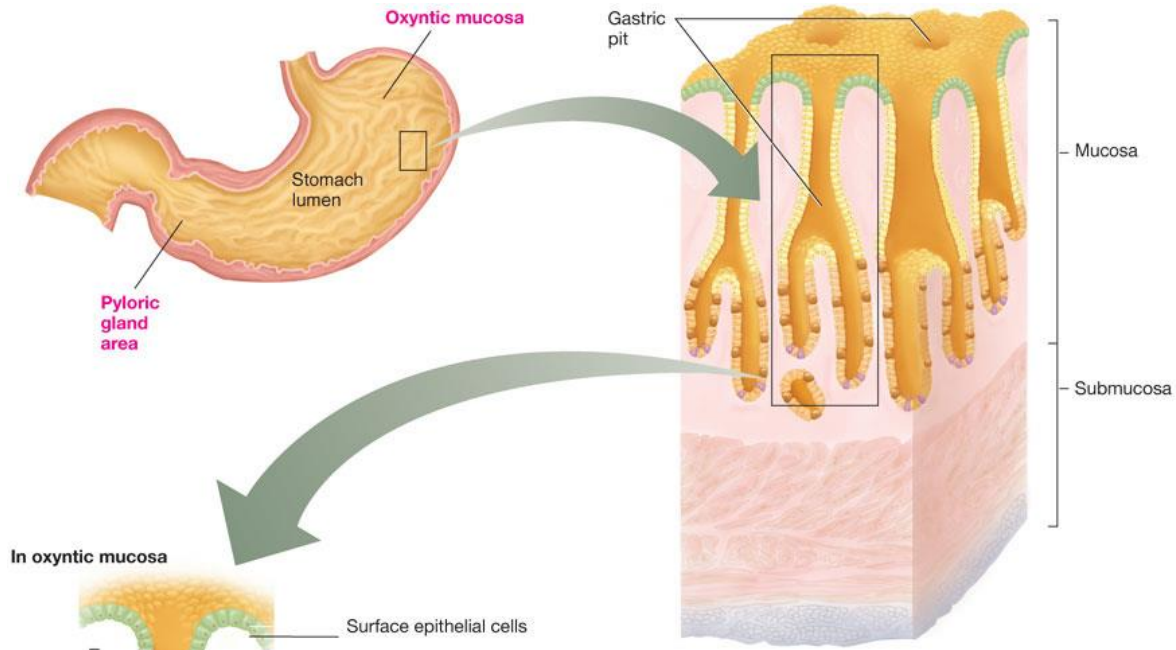


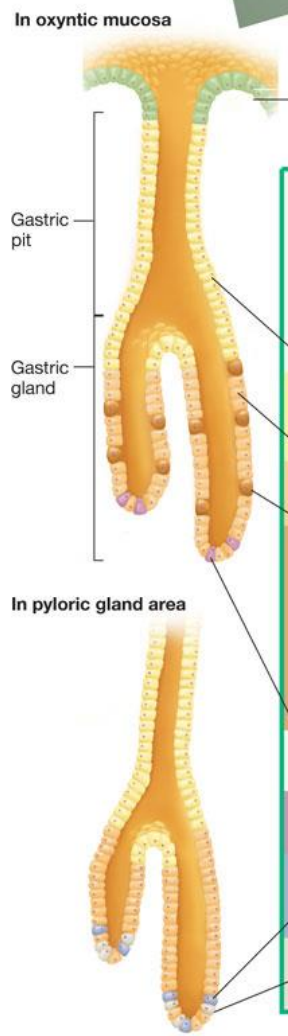
1. Gastrointestinal Tract Structure and Function

Summary of Pathways Controlling Digestive System Activities



Gastrointestinal Secretions

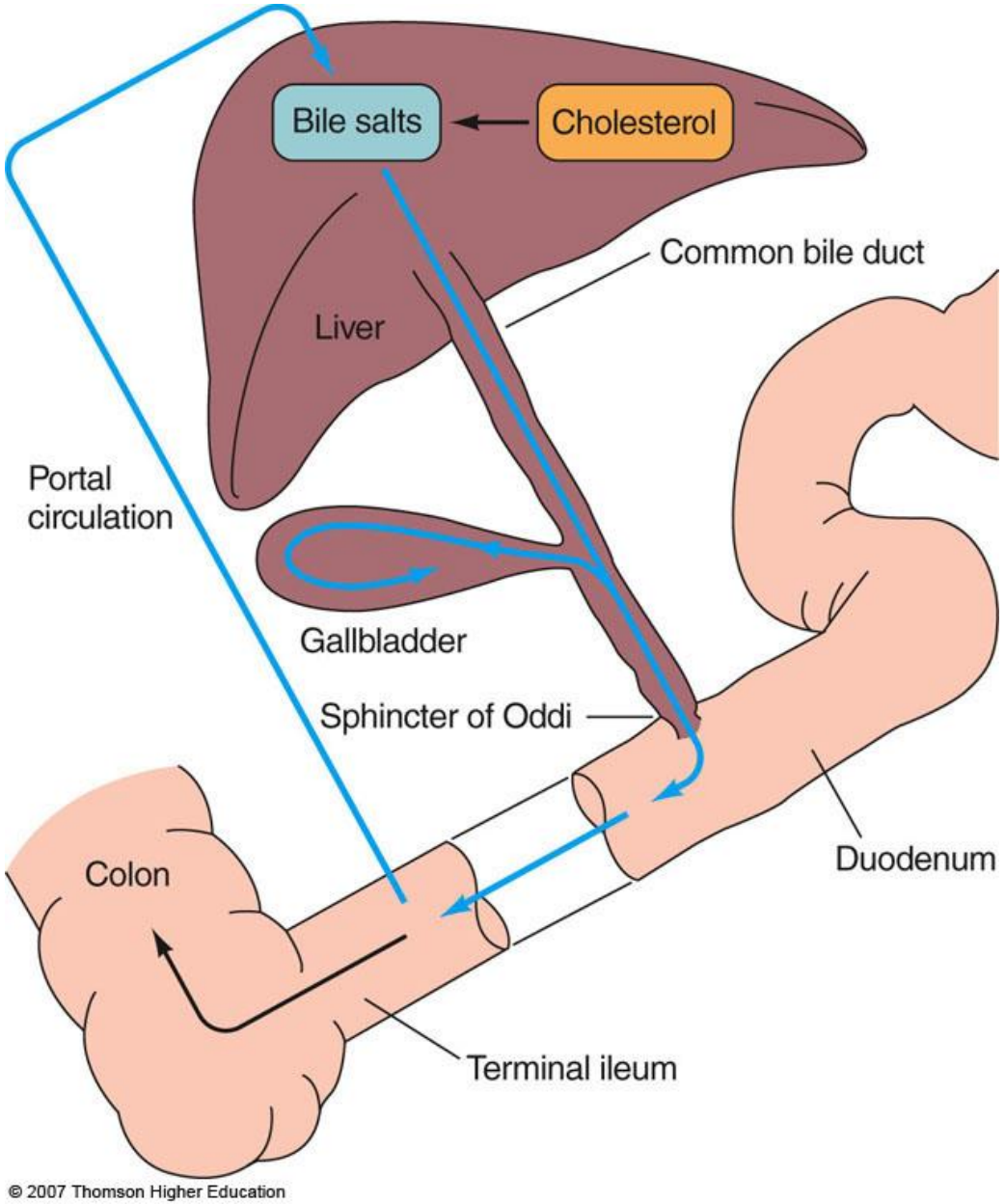




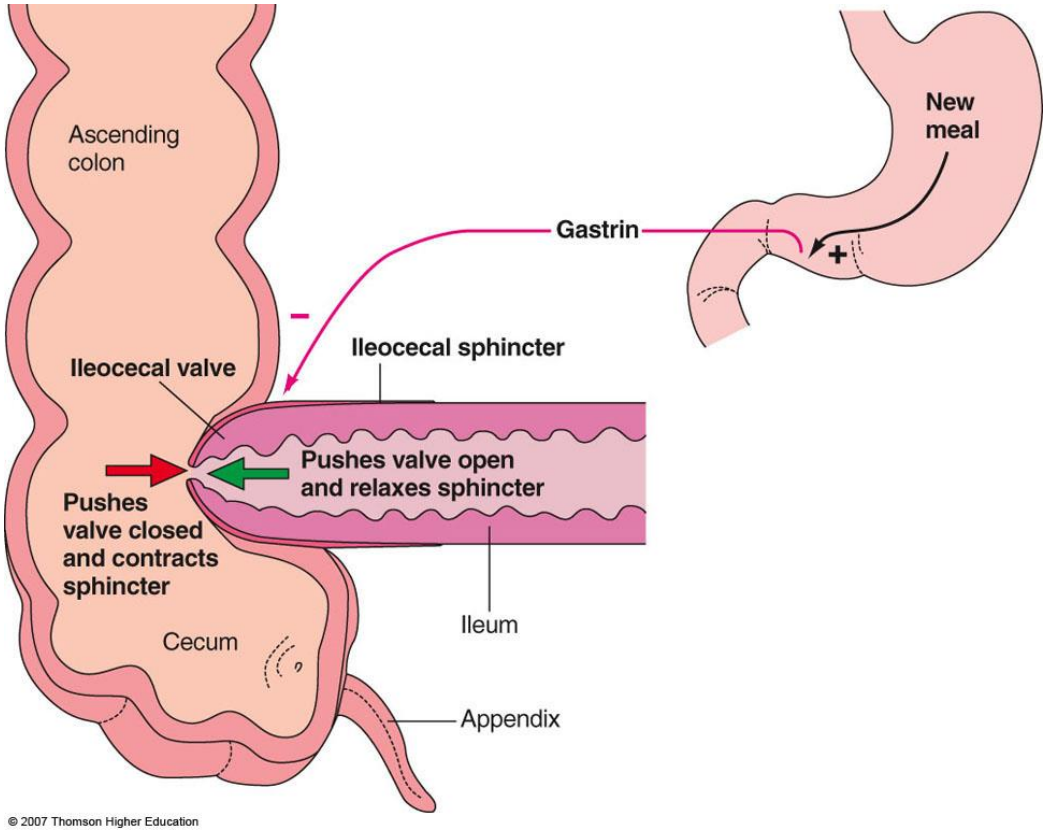
▲ **TABLE 16-4**
The Stomach Mucosa and the Gastric Glands

Type of Secretory Cell	Product Secreted	Stimuli for Secretion	Function(s) of Secretory Produd
Exocrine cells			
Mucous cells	Alkaline mucus	Mechan ical stimulation by contents	Protects mucosa against mechan ical, pepsin, and acid injury
Chief cells	Pepsinogen	ACh, gastrin	When activated, begins protein digestion
Parietal cells	Hydrochloric acid	ACh, gastrin, histamine	Activates pepsinogen, breaks down connective tissue, denatures prote ins, kills micro-organisms
	Intrinsic factor		Facilitates absorption of vitamin B_{12}
Endocrine/ paracrine cells			
Enterochromaffin-like (ECL) cells	Histamine	ACh, gastrin	Stimulates parietal cells
G cells	Gastrin	Protein products, ACh	Stimulates parietal, chief, and ECL cells
D cells	Somatostatin	Acid	Inhibits parietal, G, and ECL cells

Enterohepatic circulation of bile salts



Control of the ileocecal valve/sphincter



Major Gastrointestinal Hormones

- Gastrin
  - Release is stimulated by presence of protein in stomach
  - Secretion inhibited by accumulation of acid in stomach
  - Functions
    - Acts in several ways to increase secretion of HCl and pepsinogen
    - Enhances gastric motility, stimulates ileal motility, relaxes ileocecal sphincter, induces mass movements in colon
    - Helps maintain well-developed, functionally viable digestive tract lining

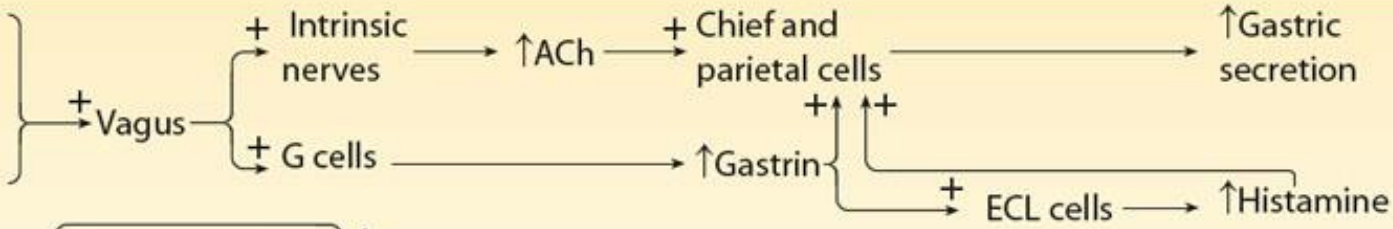
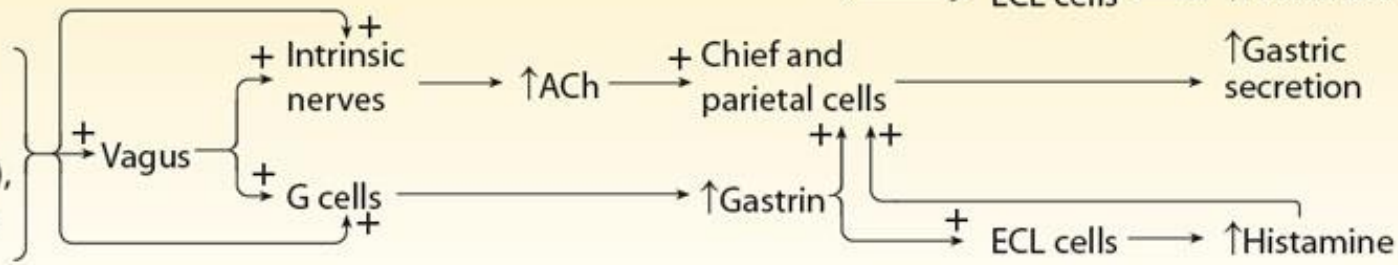
- Secretin
  - Presence of acid in duodenum stimulates release
  - Functions
    - Inhibits gastric emptying in order to prevent further acid from entering duodenum until acid already present is neutralized
    - Inhibits gastric secretion to reduce amount of acid being produced
    - Stimulates pancreatic duct cells to produce large volume of aqueous $NaHCO_3$ secretion
    - Stimulates liver to secrete $NaCO_3$ rich bile which assists in neutralization process
    - Along with CCK, is trophic to exocrine pancreas

- Cholecystokinin (CCK)
  - Functions
    - Inhibits gastric motility and secretion
    - Stimulates pancreatic acinar cells to increase secretion of pancreatic enzymes
    - Causes contraction of gallbladder and relaxation of sphincter of Oddi
    - Along with secretin, is trophic to exocrine pancreas
    - Implicated in long-term adaptive changes in proportion of pancreatic enzymes in response to prolonged diet changes
    - Important regulator of food intake

- Gastric inhibitory peptide (GIP)
  - Inhibitory effects on gastric acid secretion
  - Glucose-dependent insulinotrophic peptide
  - Stimulates insulin release by pancreas

▲ TABLE 16-4

Stimulation of Gastric Secretion

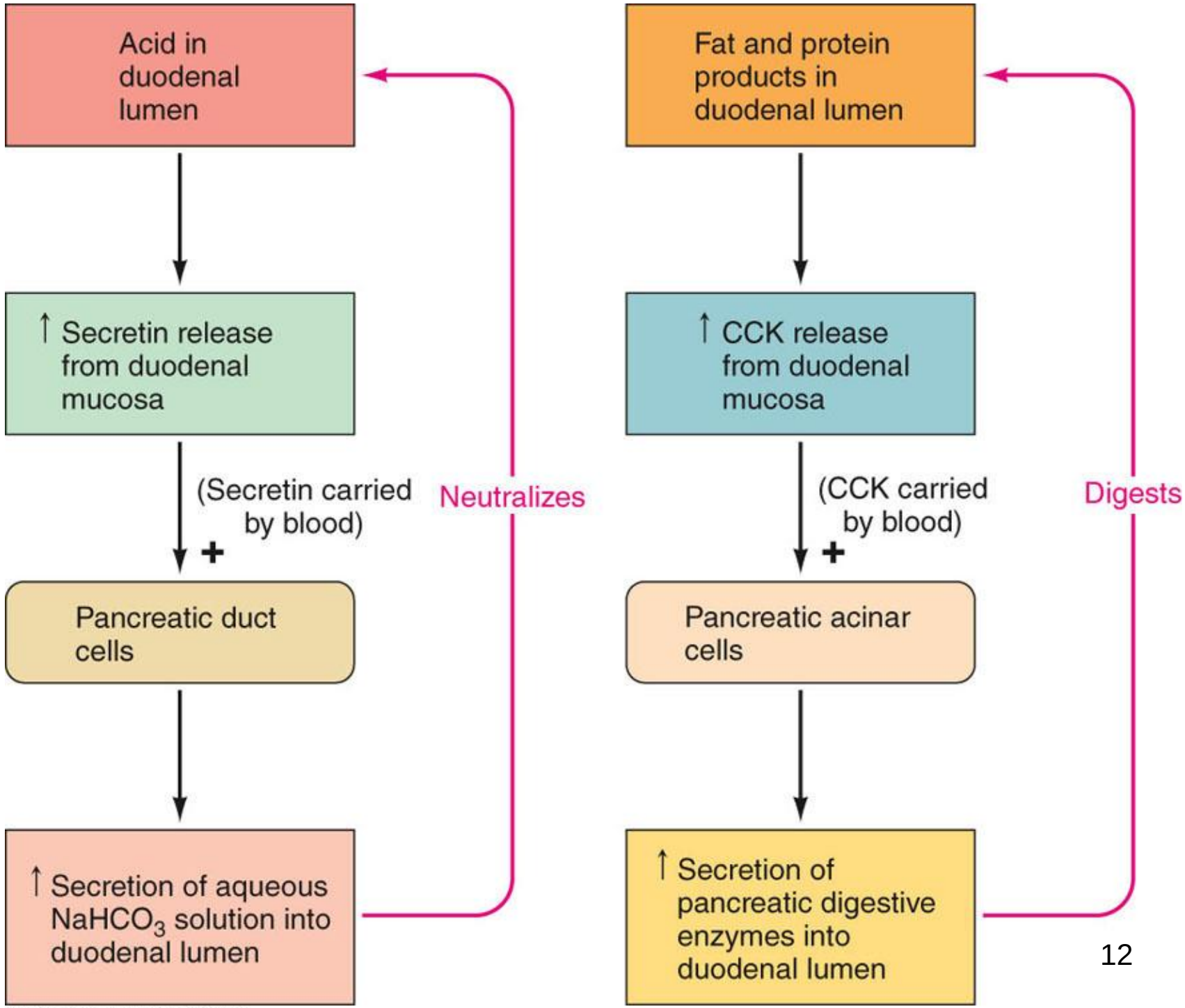
PHASE	STIMULI	EXCITATORY MECHANISM FOR ENHANCING GASTRIC SECRETION
Cephalic Phase of Gastric Secretion	Stimuli in the head—seeing, smelling, tasting, chewing, swallowing food	
Gastric Phase of Gastric Secretion	Stimuli in the stomach—protein, (peptide fragments), distension, caffeine, alcohol	

Gastric secretion gradually decreases as food empties from the stomach into the intestine.

TABLE 16-5
Inhibition of Gastric Secretion

REGION	STIMULI	INHIBITORY MECHANISM FOR GASTRIC SECRETION
Body and Antrum	Removal of protein and distension as the stomach empties	(−) Intrinsic nerves; (−) Vagus; (−) G cells → ↓Gastrin → ↓Histamine → ↓Gastric secretion
Antrum and Duodenum	Accumulation of acid	(+) D cells → ↑Somatostatin → (−) Parietal cells; (−) G cells; (−) ECL cells → ↓Gastric secretion
Duodenum (Intestinal Phase of Gastric Secretion)	Fat Acid Hypertonicity Distension	(+) Enterogastric reflex; (+) ↑Enterogastrones (cholecystokinin and secretin) → (−) Parietal cells; (−) Chief cells; (−) Smooth muscle cells → ↓Gastric secretion and motility

Hormonal control of pancreatic secretion



2. Source and Chemistry of the Gastrointestinal Hormones

- The GI hormones are synthesized within a system of clear cells (enterochromaffin, argyrophil, or argentaffin cells), so called because they are selectively stained by certain silver salts.
- These clear cells, scattered within the GI tract mucosa from the stomach through the colon, are often referred to as the diffuse or dispersed endocrine system, or, along with the pancreatic hormones, as the gastroenteropancreatic hormones.
- Enterochromaffin-like (ECL) cells

1) Gastrin hormone family members contain a biologically active C-terminal pentapeptide sequence

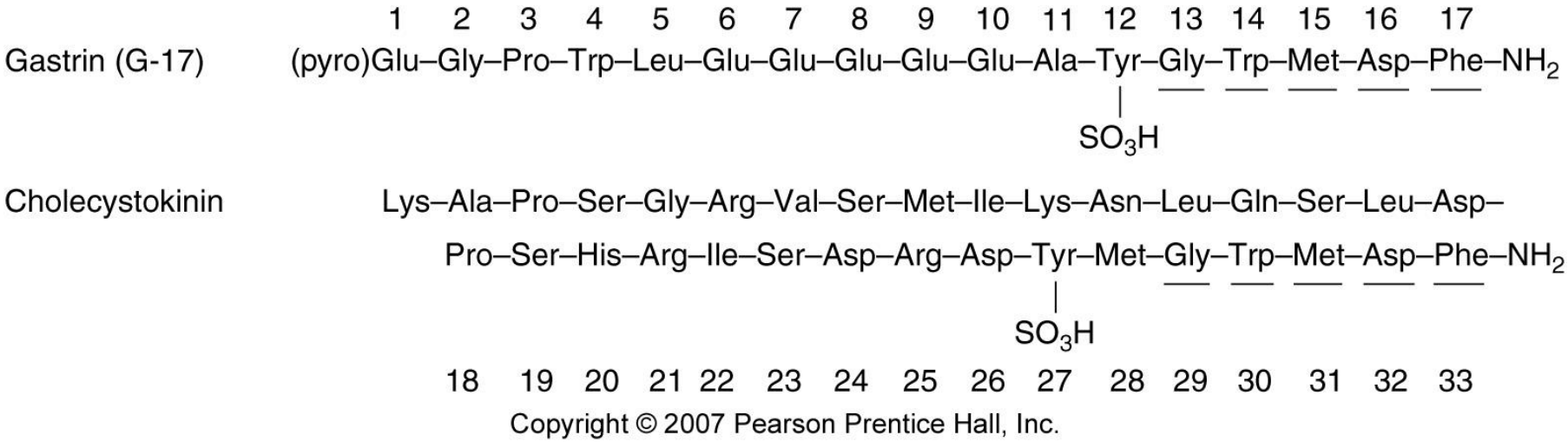


Fig. 10-1: Amino acid sequences of human G-17 gastrin and cholecystokinin (CCK). Identical C-terminal pentapeptide sequences are indicated.

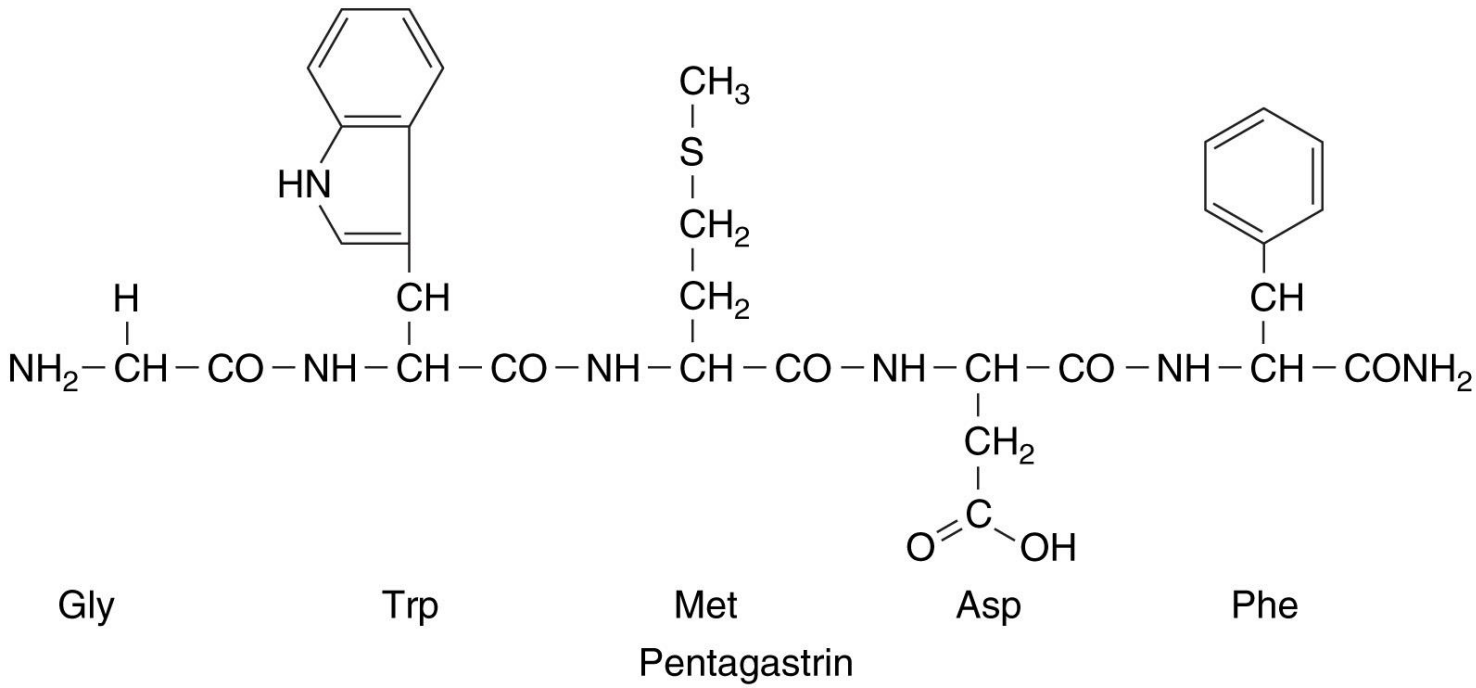


Fig. 10-2: Structure of pentagastrin.

TABLE 10.1 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(–SO_3H)–Gly–Trp–Met–Asp–Phe–NH_2
III $Gastrin_{17}$ (little gastrin)	(pyro)Glu–Gly–Pro–Trp–Leu–Glu–Glu–Glu–Glu–Glu–Ala–Tyr(–SO_3H)–Gly–Trp–Met–Asp–Phe–NH_2
IV $Gastrin_{14}$ (mini-gastrin)	Trp–Leu–Glu–Glu–Glu–Glu–Glu–Ala–Tyr(–SO_3H)–Gly–Trp–Met–Asp–Phe–NH_2

[a]Gastrin-34, G-17, and G-14 also exist without a sulfate ester at their tyrosyl residue.

2) Secretin shares partial sequence identity with glucagon, GIP and VIP

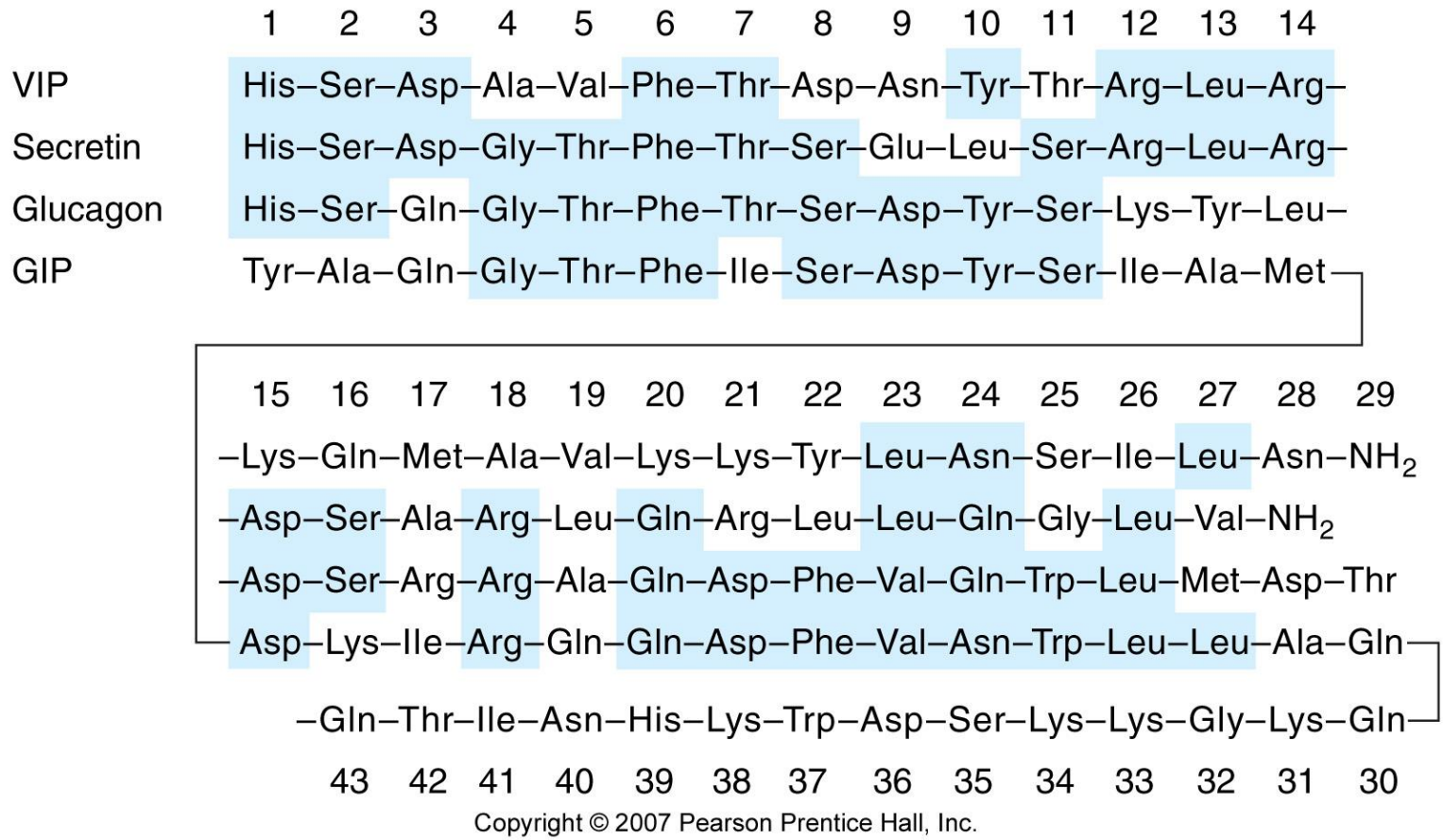


Fig. 10-3: Amino acid sequences of porcine peptides of the secretin family. Boxed areas indicate identical amino acid sequences between peptides.

3) The GI tract produces other biologically active peptides that are putative hormones

TABLE 10.2 Candidate hormones of the gut

Hormone	
Substance P	Arg–Pro–Lys–Pro–Gln–Gln–Phe–Phe–Gly–Leu–Met–NH_2
Somatostatin	Ala–Gly–Cys–Lys–Asn–Phe–Phe–Trp–Lys–Thr–Phe–Thr–Ser–Cys
Motlin	Phe–Val–Pro–Ile–Phe–Thr–-Tyr–Gly–Glu–Leu–Glu–Arg–Met–Glu–Gly–Lys–Glu–Arg–Asn–Lys–Gly–Glu
Neurotensin	(pryo)Glu–Leu–Tyr–Glu–Asn–Lys–Pro–Arg–Arg–Pro–Tyr–Ile–Leu

3. Physiological Roles of the Gastrointestinal Hormones

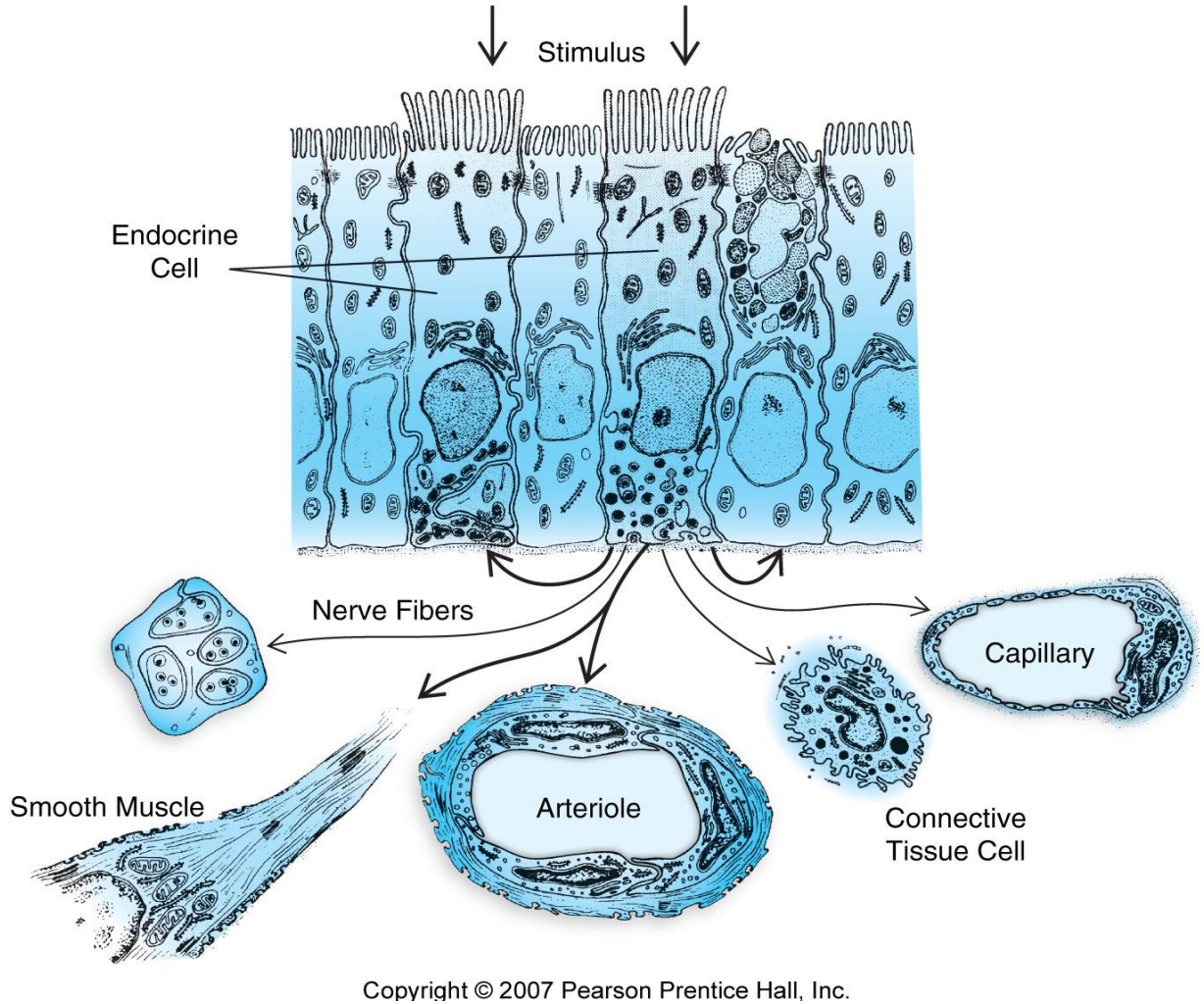
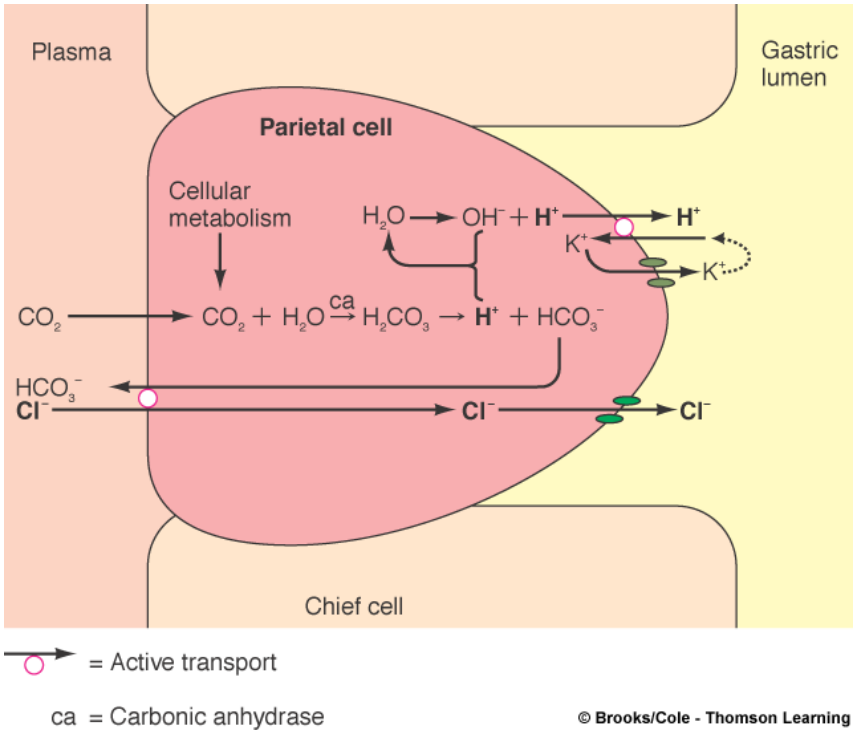
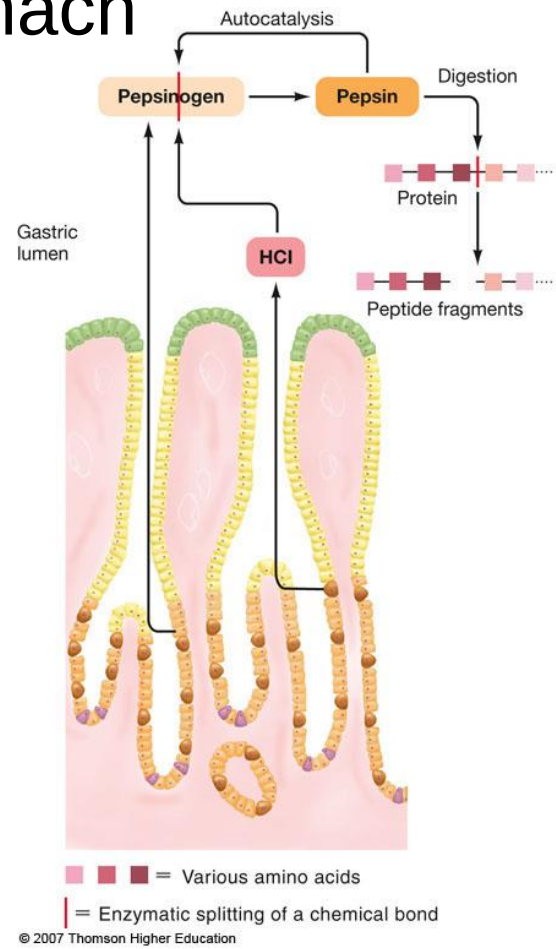


Fig. 10-4: Schematic drawing indicating the possible actions of enteroendocrine cells. The stimulus from the intestinal lumen acts on the receptors of the brush-border membrane, resulting in a release of hormones by exocytosis. The peptide hormones may exert their effect on the following: (a) adjacent epithelial cells, nerve fibers, nerve cells, smooth muscle, and connective tissue cells of the lamina propria; (b) cells of the whole organism following delivery to the systematic circulation. Method (a) is described as paracrine; method (b) is referred to as endocrine.

1) Gastrin stimulates acid secretion in the stomach





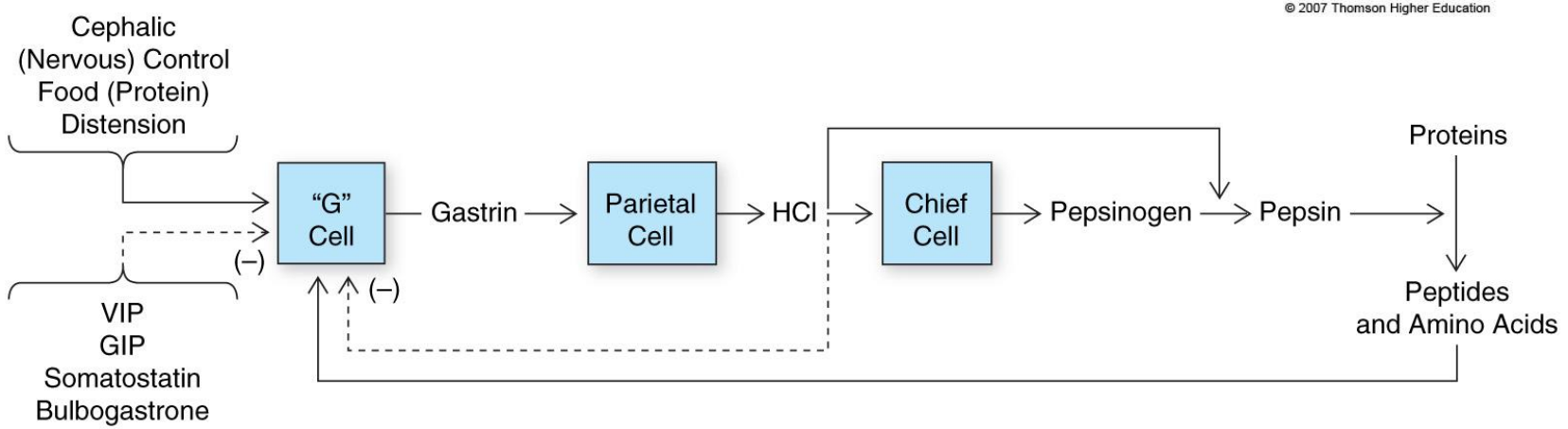
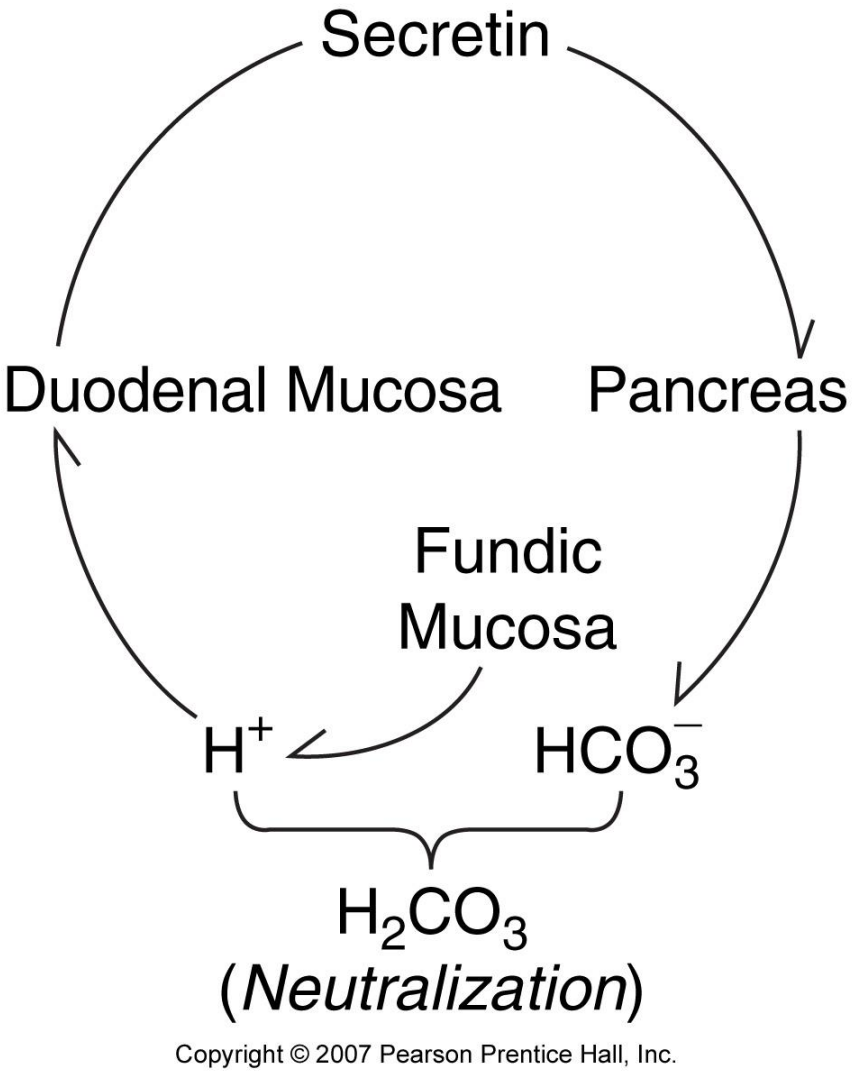


Fig. 10-5: Neuroendocrine integration of gastric acid secretion. (See also Fig. 10.14.)

2) Secretin stimulates pancreatic bicarbonate and enzyme secretions



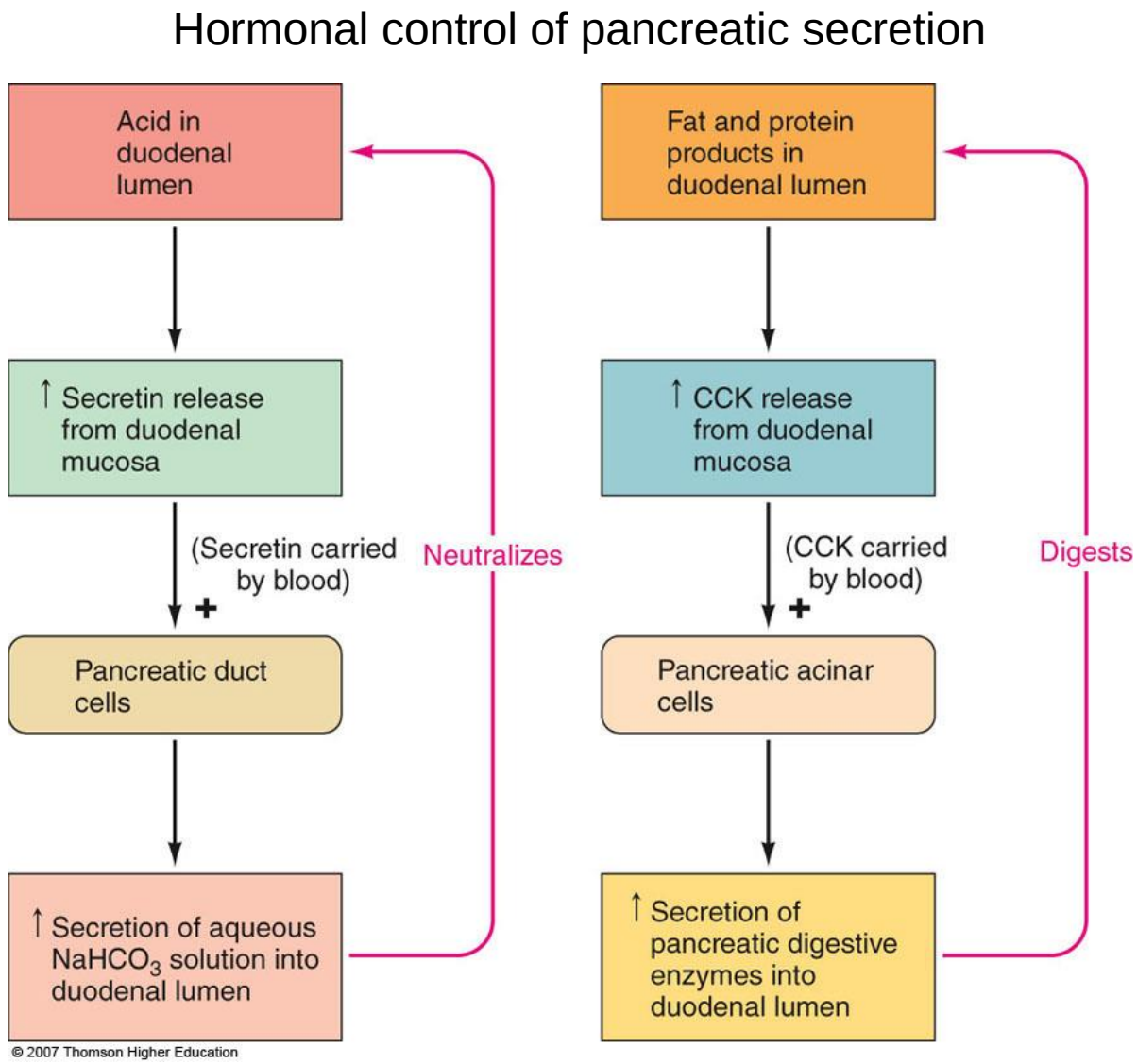
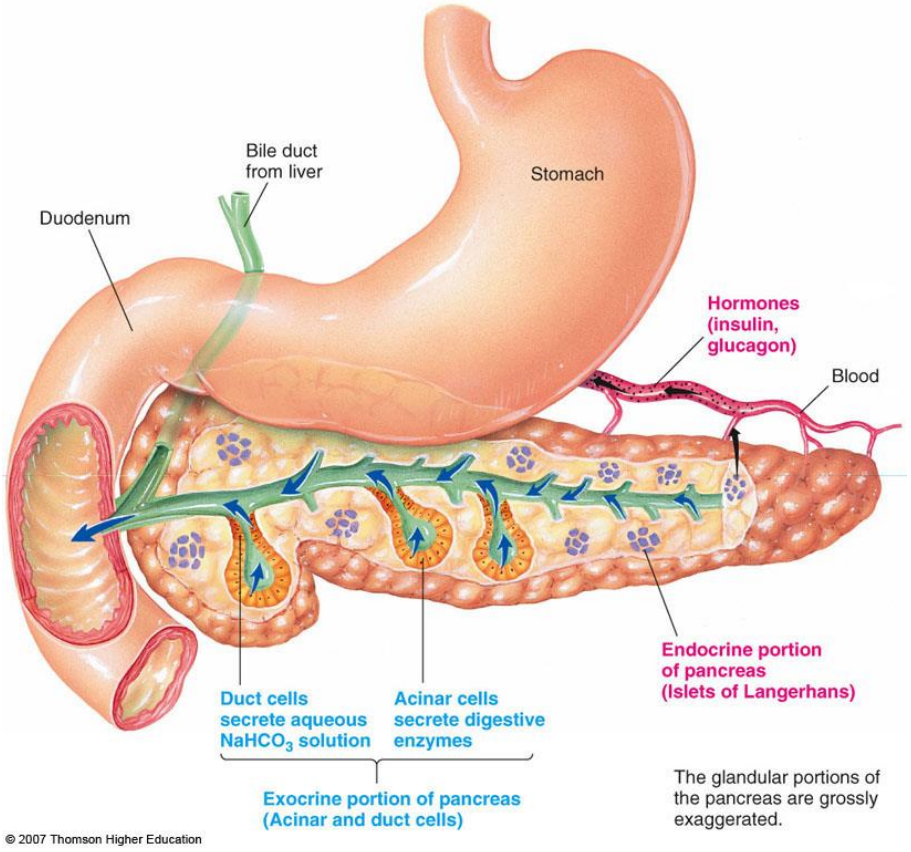


Fig. 10-6: Homeostatic closed-loop endocrine mechanism of small intestine pH control.

3) CCK stimulates gallbladder contraction and pancreatic enzyme secretions



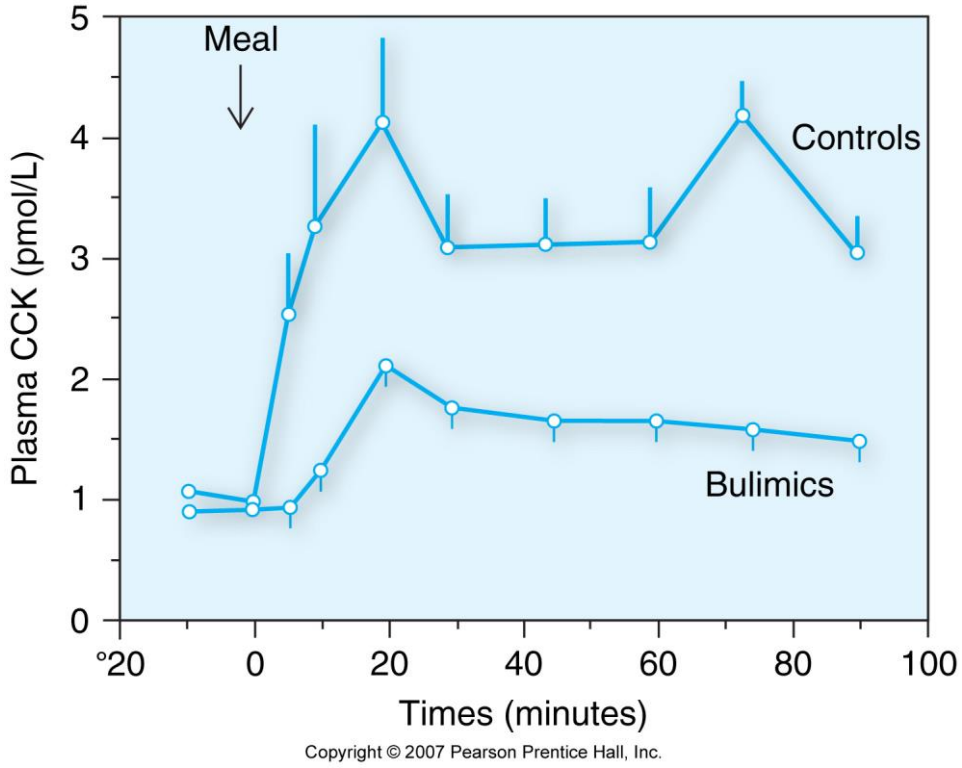


Fig. 10-7: Plasma cholecystokinin (CCK) responses to a meal in normal subjects and patients with bulimia (uncontrollable eating). After an overnight fast, 14 patients with bulimia and 10 age- and sex-matched normal volunteers were fed a 400 ml mixed-liquid meal. Plasma was collected and extracted at the indicated times and assayed for CCK bioactivity, expressed as cholecystokinin-8 equivalents. Values are means ± SEM. The arrow indicates the beginning of the meal.

4) Gastric inhibitory peptide (GIP) inhibits gastric emptying and gastric acid secretion.
   - 43-aa peptide
   - Inhibitory effects on gastric acid secretion
   - Glucose-dependent insulinotrophic peptide
   - Stimulates insulin release by pancreas
5) Glucagon-like peptide-1 (GLP-1) stimulates insulin secretion and inhibits glucagon secretion
6) Vasoactive intestinal peptide (VIP) inhibits gastric acid secretion and stimulates pancreatic electrolyte and water secretion
7) Neurotensin stimulates pancreatic secretion and inhibits gasrtic motility.
8) Peptide YY inhibits pancreatic bicarbonate secretion, gallbladder contraction, and gastric emptying.

9) Substance P (SP) may serve as a physiological modulator of intestinal smooth muscle contractility.

10) Somatostain inhibits gastrin and hydrochloric acid release.

11) Gastrin-releasing peptide (GRP) stimulates release of several GI hormones, pancreatic secretion, and motility.

12) Motilin stimulates GI motility and emptying of chyme into the small intestine.

13) Ghrelin is a multifunctional peptide that stimulates gastric acid secretion and gastric motility.

14) Other putative gut hormones exert specific actions in the GI tract.

- Urogastrone/EGF
- Villikinin
- Enkephalins
- Hormones in milk

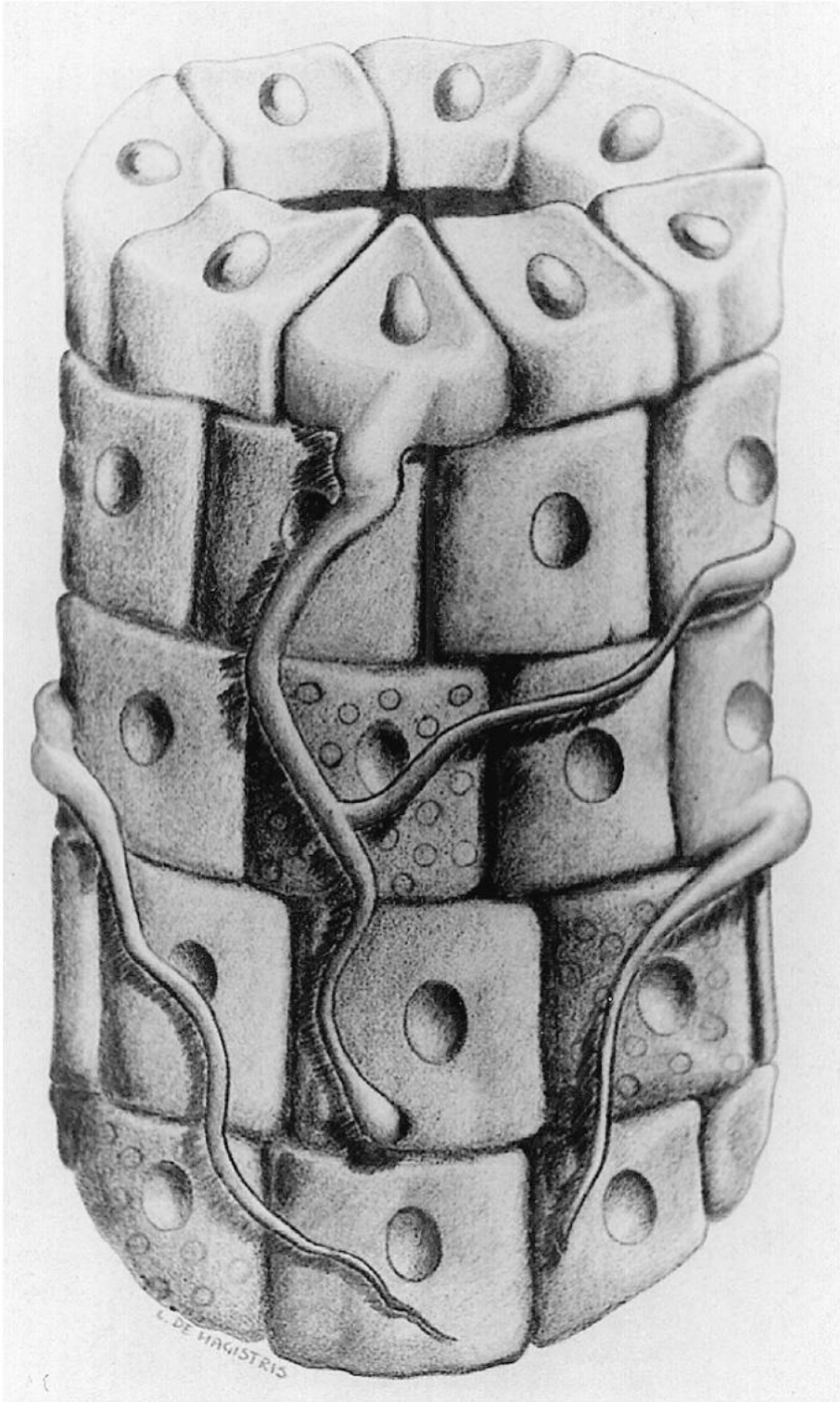


Fig. 10-9: Schematic drawing showing a three-dimensional arrangement of the somatostatin cells and their processes in an antral gland.

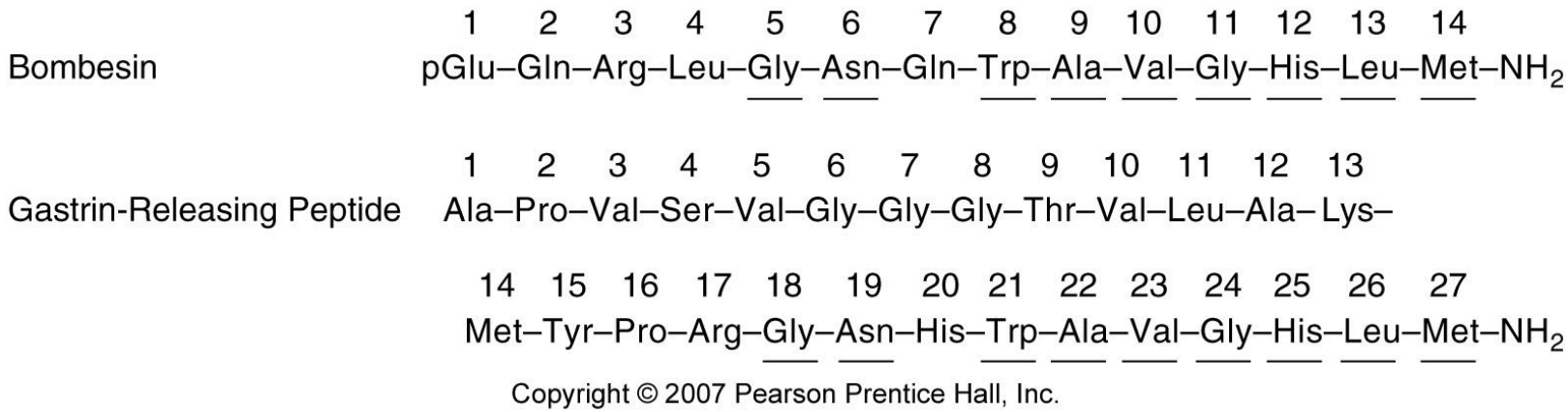


Fig. 10-10: Primary structures of bombesin and porcine gastrin-releasing peptide (GRP).

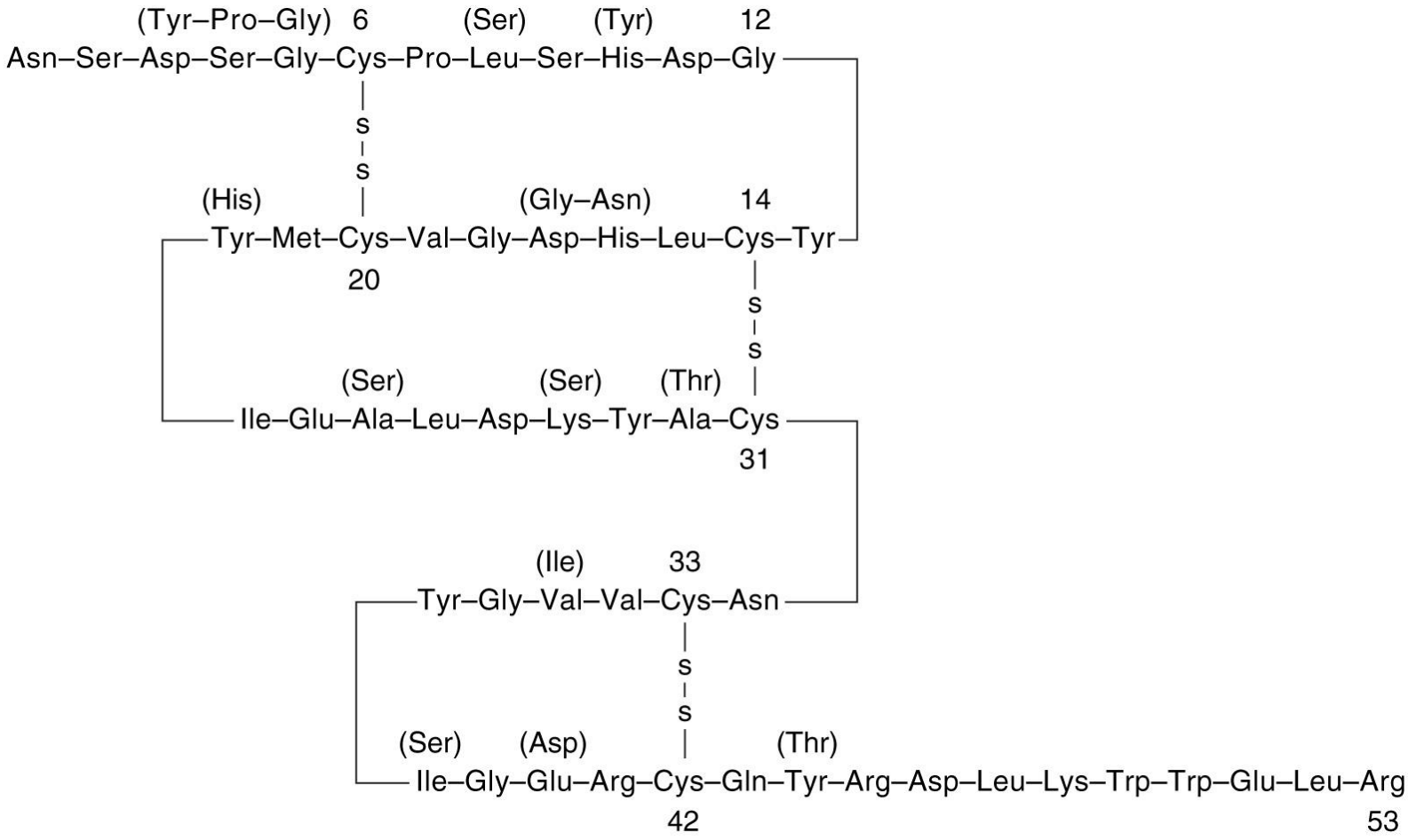


Fig. 10-11: Amino acid sequence of human β-urogastrone. Positional amino acid differences between β-urogastrone and mouse EGF are shown in parentheses.

4. Gastrointestinal Hormone Mechanisms of Action

1) Integrated actions of gastrin, acetylcholine, and histamine control gastric acid secretion

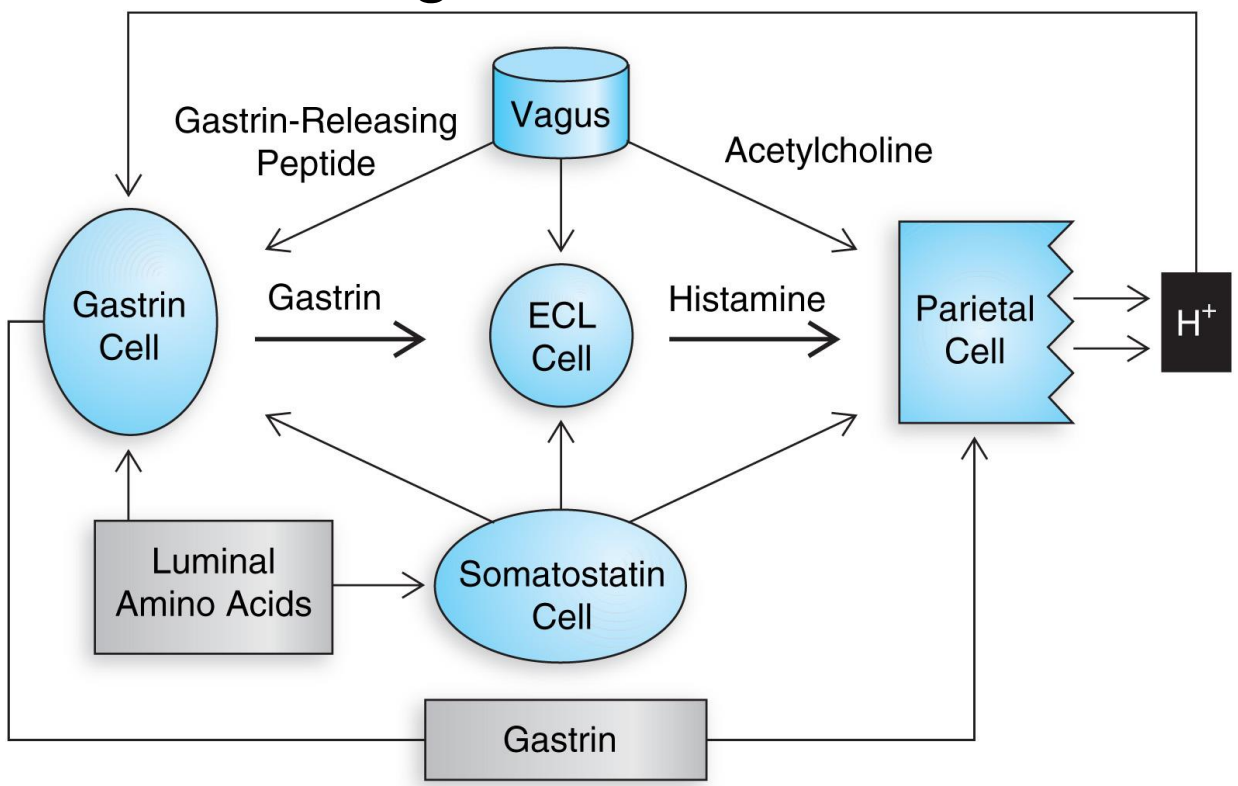


Fig. 10-12: This diagram represents the interaction of the gastrin, enterochromaffin-like (ECL), parietal, and somatostatin cells. Both antral and fundic somatostatin cells appear to exert inhibitory influences on gastrin, ECL, and parietal cells, respectively. Neurotransmitter substances from either the vagus or the intrinsic gastric neural system are responsible for modulation of each of the cells and their secretory activity. Luminal amino acids stimulate gastrin release, whereas luminal protons inhibit gastrin release. Systemic secretion of gastrin primarily drives ECL cells to secrete histamine but may play some part in parietal cell secretion, although a trophic regulatory effect is more likely. The ECL cells release histamine, which presumably functions in a paracrine fashion to stimulate parietal cell secretion. Inhibitory actions of hormones are noted (–).

2) Synergistic actions of secretin and CCK control exocrine pancreatic secretion

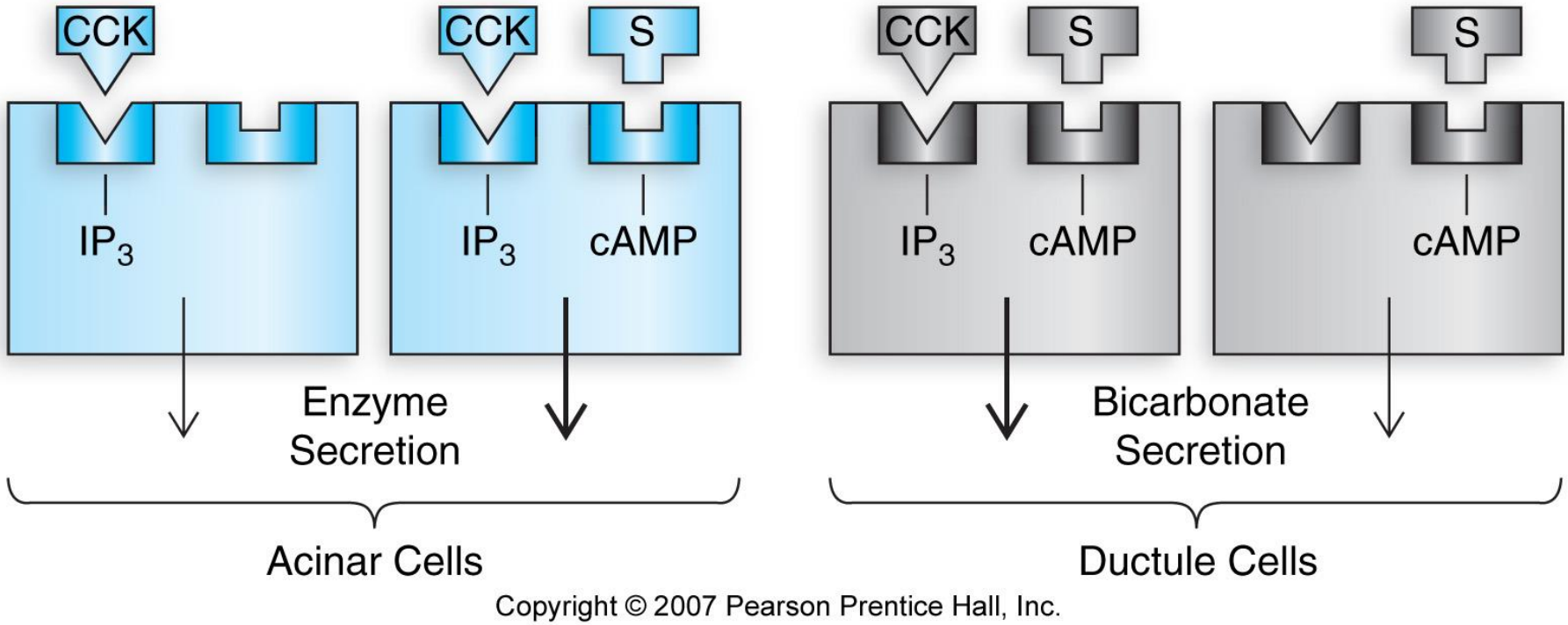


Fig. 10-13: Hypothetical model for the synergistic actions of CCK and secretin (S) and second messengers on pancreatic enzyme and bicarbonate secretion.

5. Summary of the Neuroendocrine Control of GI Function

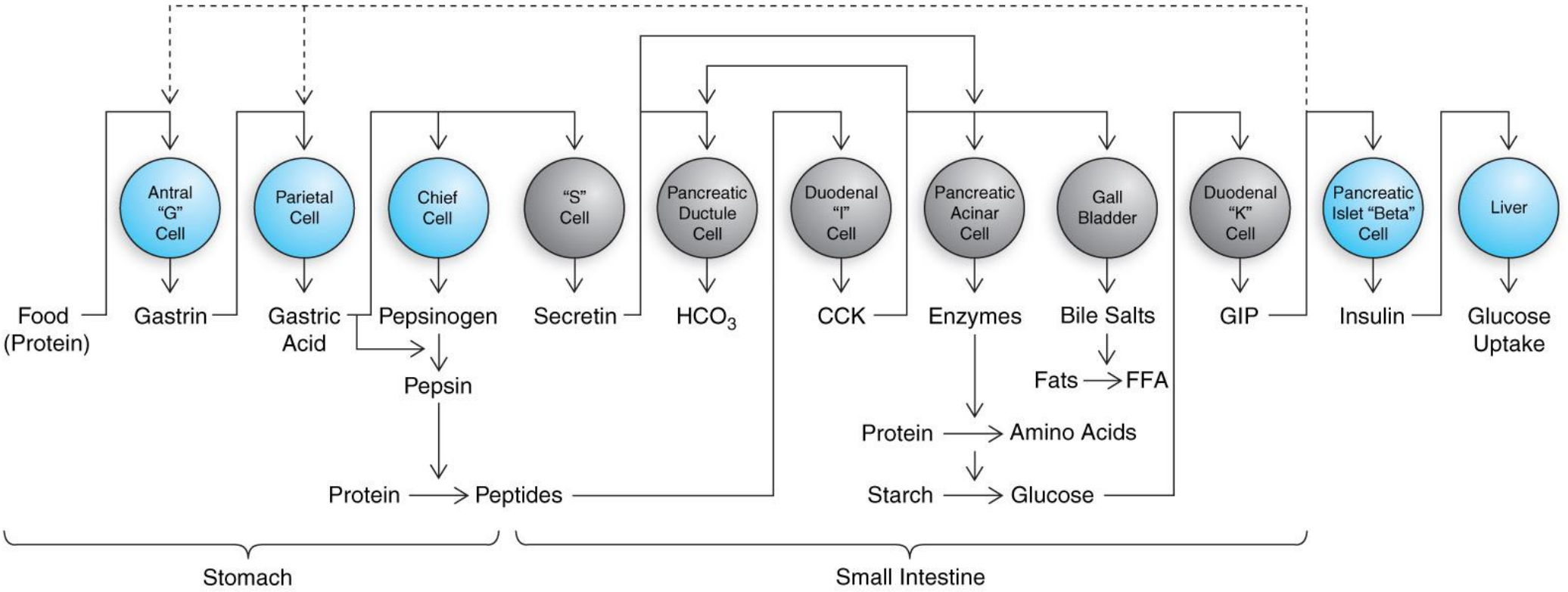


Fig. 10-14: Summary scheme of hormone-metabolite control of GI function. Solid lines indicate stimulatory influences; dashed lines represent inhibitory stimuli.

6. Pathophysiology

TABLE 10.3 Physiological roles or effects of the GI hormones and candidate hormones within the GI tract

Hormone	Physiological roles*
Gastrin	↑ gastric acid selection, gastrointestinal growth, and antral motility
Secretin	↑ pancreatic and biliary bicarbonate secretion; ↑ CCK-stimulated pancreatic enzyme secretion
CCK	↑ gallbladder contraction and pancreatic enzyme secretion; ↓ gastric emptying; ↑ growth of the exocrine pancreas, satiety signal
GIP	↓ gastric acid secretion; ↑ glucose-mediated insulin release
Somatostatin	↓ antral gastrin secretion
VIP	↑ smooth muscle relaxation; ↑ blood flow and intestinal secretion
Gastrin-releasing peptide (GRP)	↑ gastrin secretion, gallbladder contraction, pancreatic enzyme secretion, and gastrointestinal motility; ↓ gastric acid secretion (when delivered intracisternally)
Bulbogastrone	↓ gastric acid secretion
Urogastrone	↓ gastric acid secretion; ↑ oxyntic gland growth
Enteroglucagon	Unknown
Villikinin	↑ villous movement and lymph flow
Enkephalins	Unknown (neuromodulator?) ↑ or ↓ gastric acid secretion
Neurotensin	Unknown (neuromodulator?)
Substance P	Unknown, possibly modulates gut motility and mucosal secretions
Motilin	↑ gastrointestinal motility
Histamine	↑ gastric acid secretion by parietal cells
Prostaglandins	↑ mucus production by the stomach

*Arrows indicate increased/stimulated (↑) or decreased/inhibited (↓) activity in response to the hormone.

TABLE 10.4 Endocrine pathophysiology of GI disorders

Achalasia
Failure of gastroesophageal sphincter to relax (and food accumulates in the esophagus). May be due to smooth muscle hypersensitivity to gastrin.

Anorexia nervosa
Decreased desire to eat. Possibly due to increased CCK secretion or increased sensitivity to CCK. May also relate to decreased appetite in aging individuals.

Bulimia nervosa
Recurrent episodes of uncontrolled eating. Possibly due to lowered CCK secretion.

Cholera
Cholera toxin irreversibly activates intestinal cell adenylate cyclase. This results in enhanced intestinal fluid secretion leading to dehydration and death if not corrected.

Chronic idiopathic* constipation
Possibly due to elevated circulating levels of motilin.

Disordered gastric emptying
Possibly due to hypopyloric valve dysfunction.

Gastric (peptic) ulcers
Multiple causes: enhanced HCl secretion resulting from increased parietal cell stimulation (e.g., by gastrin as in gastrinemia); decreased PGE_2 secretion resulting in: (a) increased HCl secretion, (b) decreased mucus production (e.g., as induced by aspirin) resulting in epithelial-cell damage by HCl; enhanced vagal (cholinergic stimulation; enhanced histamine secretion; etc.).

Gastrin and cancer
Gastrin may be a trophic factor for several cancer cells, and gastrin receptors have been identified in colonic mucosa, adenocarcinoid, and pancreatic tumor cells.

Gastroesophageal reflux
Possibly due to hypogastrinemia and low pressure.

Hypergastrinemia (Zollinger–Ellison syndrome)
Type I: G-cell hyperplasia (may be due to hypochlorhydria/achlorhydria due to pernicious anemia).
Type II: Gastrinoma (gastrinoma syndrome).

Hypochlorhydric disease states
Pernicious anemia is the result of an autoimmune process in which the gastric fundus undergoes atrophy and parietal cells are destroyed. (Achlorhydric anemia: lowered levels of gastric acid result in enhanced, uninhibited, gastrin secretion. This results in hypertrophy and hyperplasia of ECL cells, often resulting in neoplasia.)

Idiopathic delay in gastric emptying
Possibly as directly above.

Pancreatic cholera (watery diarrhea syndrome)
Due to excess VIP secretion (VIPoma syndrome).

* Idiopathic: "Without clear pathogenesis or disease without recognizable cause, as if of spontaneous origin."