Varastegan
Institute for Medical Sciences

Digestion, Absorption, Transport, and Excretion of Nutrients

(Session 2)

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Regulators of Gastrointestinal Activity: Nerves, Neurotransmitters, and Neuropeptide Hormones

Neural Mechanisms

GI movement, results from the coordinated activity of enteric nerves, extrinsic nerves, endocrine cells, and smooth muscle.

The neural mechanisms include:

(1) An intrinsic system consisting of two layers of nerves embedded in the gut wall

(2) An external system of nerve fibers running to and from the central and autonomic nervous systems

Mucosal receptors in the gut are sensitive to the composition of the chyme and lumen distention and send impulses through submucosal and mesenteric nerves.

The Brain in Your Gut

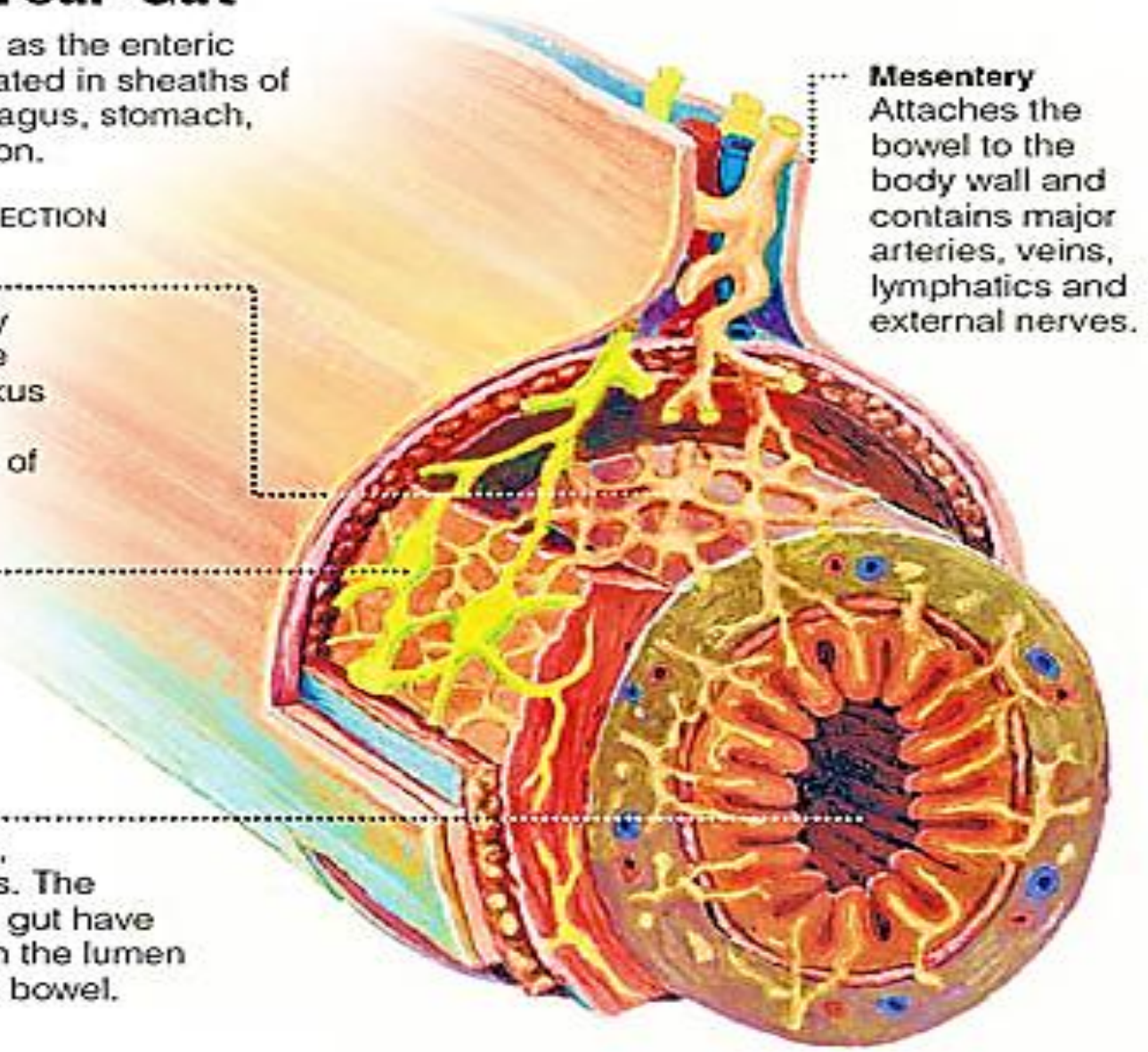
The gut's brain, known as the enteric nervous system, is located in sheaths of tissue lining the esophagus, stomach, small intestine and colon.

SMALL INTESTINE CROSS SECTION

Submucosal plexus Layer contains sensory cells that communicate with the myenteric plexus and motor fibers that stimulate the secretion of fluids into the lumen.

Myenteric plexus Layer contains the neurons responsible for regulating the enzyme output of adjacent organs.

Lumen No nerves actually enter this area, where digestion occurs. The brains in the head and gut have to monitor conditions in the lumen across the lining of the bowel.



Mesentery Attaches the bowel to the body wall and contains major arteries, veins, lymphatics and external nerves.

Neurotransmitters and neuropeptides signal nerves to contract or relax muscles, increase or decrease fluid secretions, or change blood flow.

The GIT then largely regulates its own motility and secretory activity, however, signals from the central nervous system can override the enteric system and affect GI function.

TABLE 1-2

Examples of Neurotransmitters and Their Actions

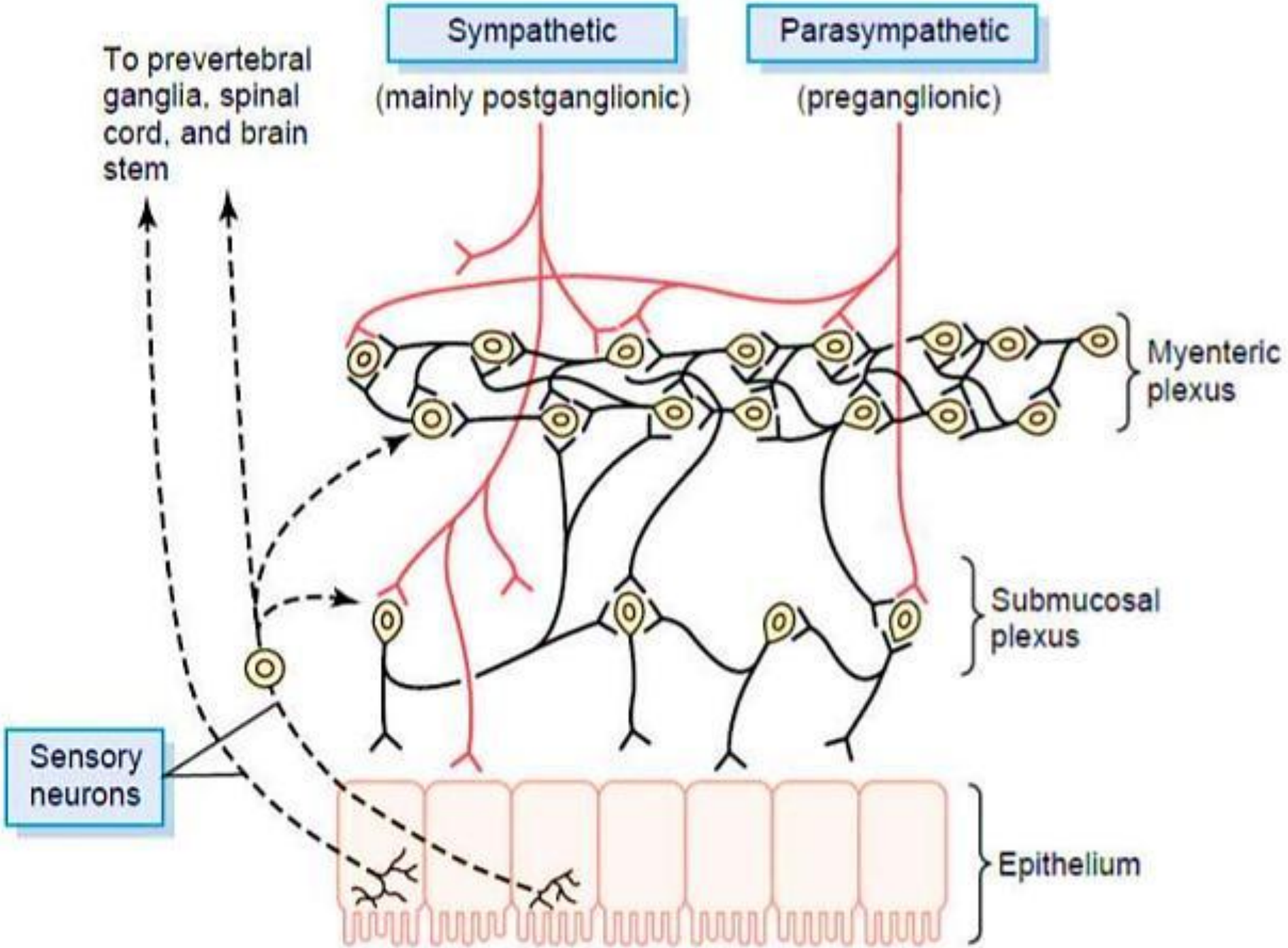
Neurotransmitter	Site of Release	Primary Action
GABA	Central nervous system	Relaxes lower esophageal sphincter.
Norepinephrine	Central nervous system, spinal cord, sympathetic nerves	Decreases motility, increases contraction of sphincters, inhibits secretions.
Acetylcholine	Central nervous system, autonomic system, other tissues	Increases motility, relaxes sphincters, stimulates secretion.
Neurotensin	GI tract, central nervous system	Inhibits release of gastric emptying and acid secretion.
Serotonin (5-HT)	GI tract, spinal cord	Facilitates secretion and peristalsis.
Nitric oxide	Central nervous system, GI tract	Regulates blood flow, maintains muscle tone, maintains gastric motor activity.
Substance P	Gut, central nervous system, skin	Increases sensory awareness (mainly pain), and peristalsis.

In people with GI disease (e.g. infections, inflammatory bowel disease, irritable bowel syndrome), the enteric nervous system may be overstimulated, resulting in abnormal secretion, altered blood flow, increased permeability, and altered immune function.

Autonomic innervation of GIT is supplied by the sympathetic fibers and by the parasympathetic fibers in the vagal and pelvic nerves.

Sympathetic neurons, tend to slow transit of GI contents by inhibiting neurons affecting secretions and muscle contractions.

On the other hand, for example, the sight or smell of food stimulates vagal activity and subsequent secretion of acid from parietal cells scattered along the walls of the stomach.


Sympathetic
(mainly postganglionic)
Parasympathetic
(preganglionic)
To prevertebral ganglia, spinal cord, and brain stem
Myenteric plexus
Submucosal plexus
Sensory neurons
Epithelium

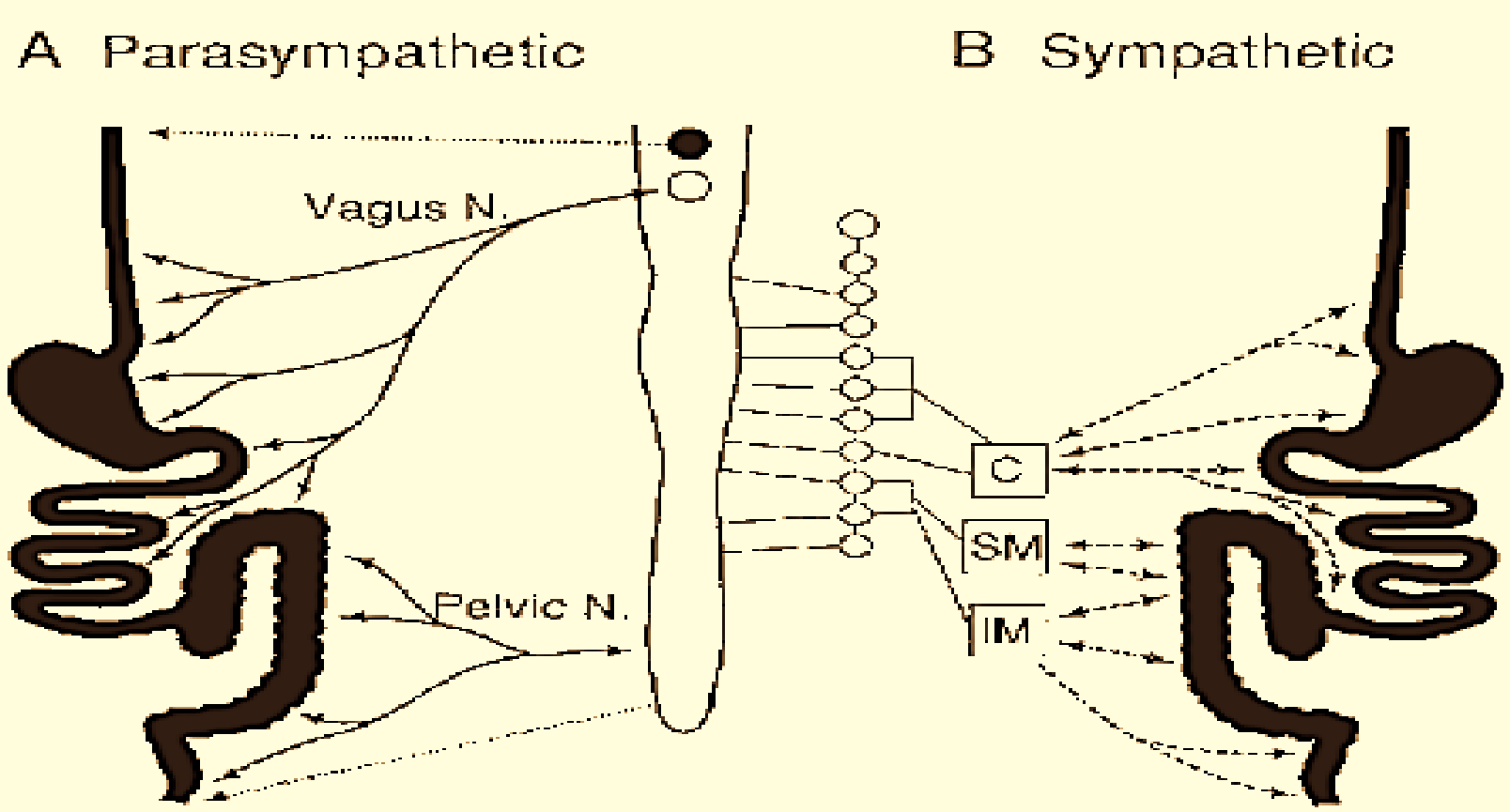
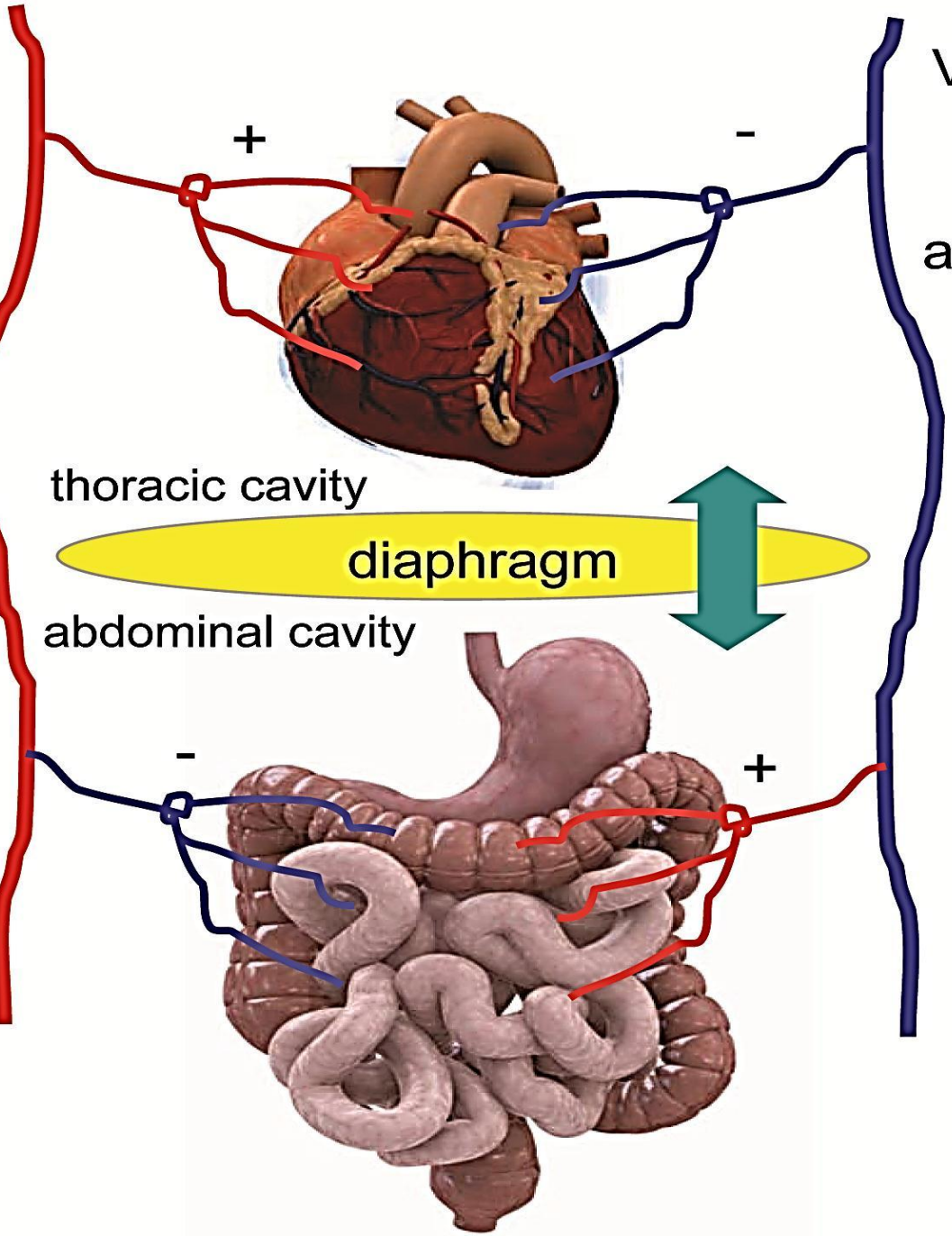


Fig. 42.7. The extrinsic branches of the autonomic nervous system. **A.** Parasympathetic. *Dashed lines* indicate cholinergic innervation of the striated muscle in the esophagus and external anal sphincter. *Solid lines* indicate afferent and preganglionic innervation of the remaining gastrointestinal tract. **B.** Sympathetic. *Solid lines* denote the afferent and preganglionic efferent pathways between the spinal cord and the prevertebral ganglia. *Dotted lines* indicate the afferent and postganglionic efferent innervation. *C*, celiac; *IM*, inferior mesenteric; *SM*, superior mesenteric. (Reprinted with permission from Johnson LR, Alpers DH, Jacobson ED et al, eds. Physiology of the Gastrointestinal Tract, vol 1. 3rd ed. New York: Raven Press, 1994:451.)

Sympathetic nerve endings secrete nor-epinephrine activating adrenergic receptors, stimulating cardiac activity; yet inhibiting gastrointest-nal activity.



Vagus nerve endings secrete acetylcholine activating cholinergic receptors, inhibiting cardiac activity yet stimulating gastro-intestinal activity.

Primary Neuropeptide Hormones

Regulation of the GIT activity involves numerous peptide hormones that can act in an autocrine, paracrine, or endocrine role.

Some of these hormones (e.g. of the cholecystokinin [CCK] and somatostatin family) also serve as neurotransmitters between neurons (i.e. neurocrine role).

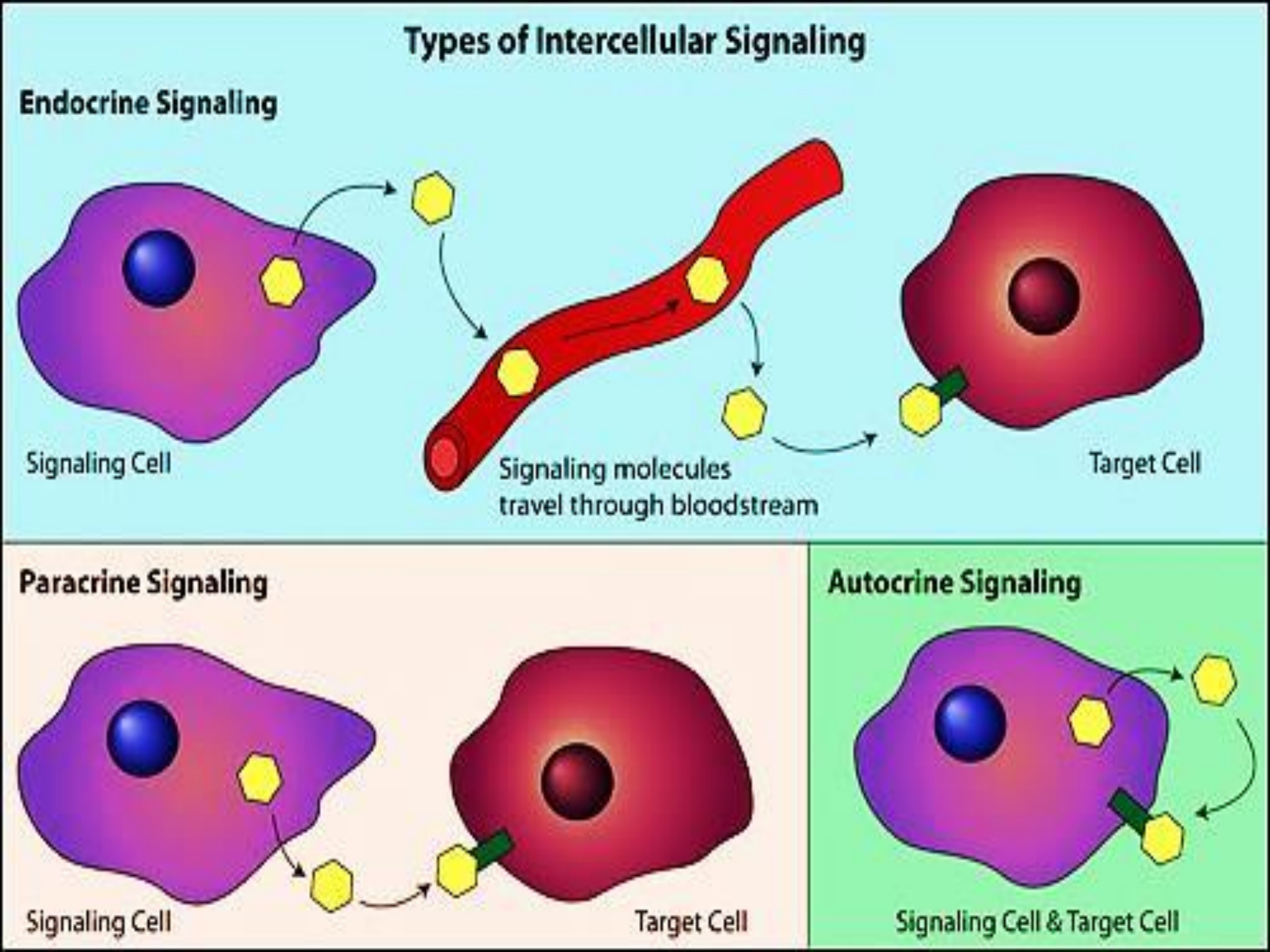
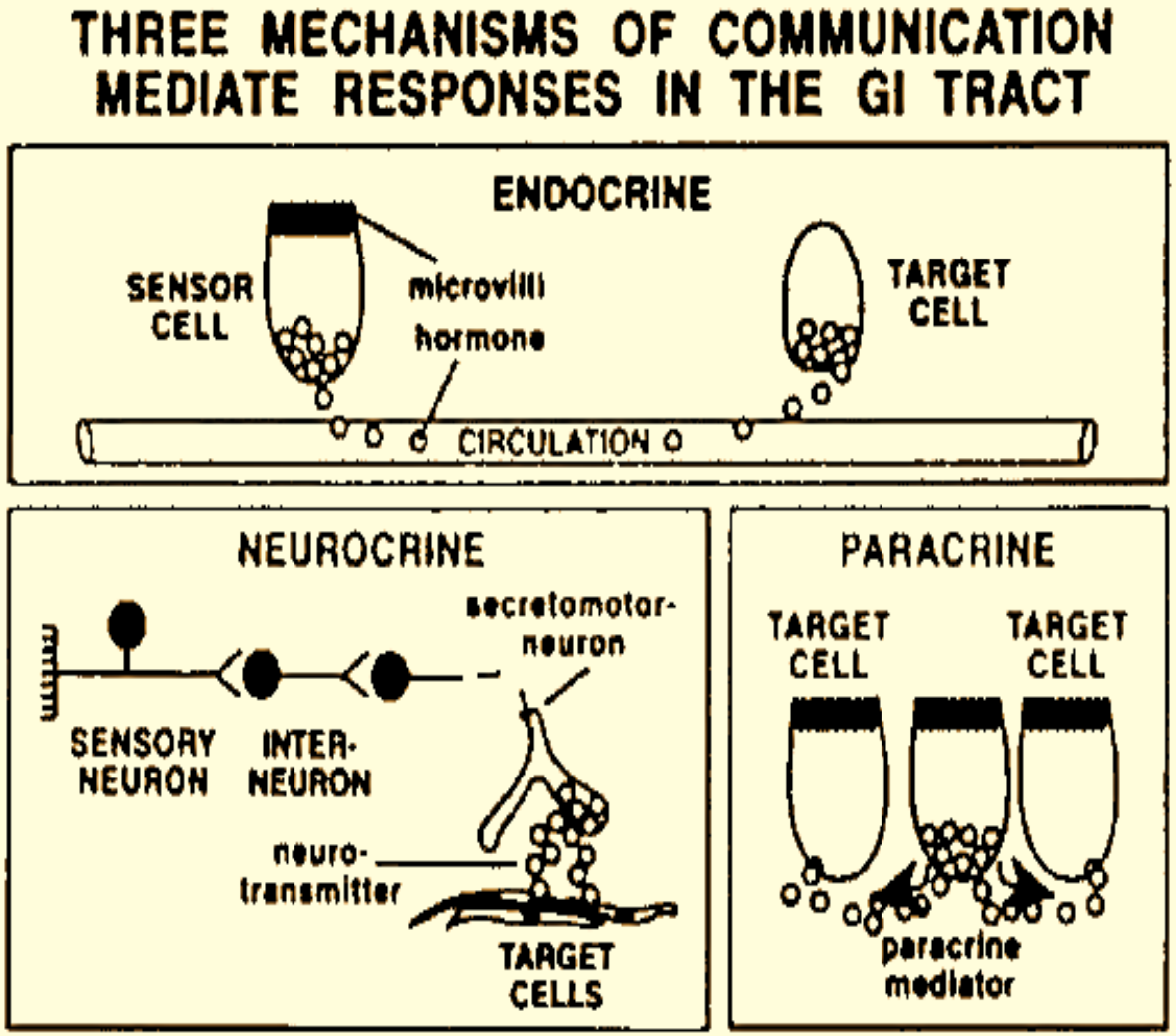

Types of Intercellular Signaling
Endocrine Signaling
Signaling Cell
Signaling molecules travel through bloodstream
Target Cell
Paracrine Signaling
Signaling Cell
Target Cell
Autocrine Signaling
Signaling Cell & Target Cell

Fig. 42.9. Three mechanisms of communication mediate responses in the gastrointestinal (GI) tract. The three mechanisms of communication that mediate responses are endocrine, neurocrine, and paracrine. For the endocrine mechanism, sensory cells respond to stimuli by releasing transmitters that travel by way of the blood to their target cells or tissues. Many examples of endocrine sensory cells through the GI tract respond to either mechanical or chemical stimuli to release their hormones. Some types of endocrine cells respond to changes in pH or osmolality, whereas others respond to changes in specific nutrients. For the neurocrine mechanisms, the sensing and transmissions to the target tissue are completely mediated by nerves and neurotransmitters. Nerves sense stimuli such as nutrients, pH, and osmolality in the luminal contents, as well as movement of the contents and distention of the gut lumen. (Reprinted with permission from Raybould H, Pandol SJ. Integrated Response to a Meal. Undergraduate Teaching Project, Unit 29. Bethesda, MD: American Gastroenterological Association, 1995.)



The GIT secretes more than 30 families of neuropeptide hormones and is the largest endocrine organ in the body.

GI hormones are involved in initiating and terminating feeding, bringing on sensations of hunger and satiety, increasing or decreasing movements of the GIT, enhancing or retarding esophageal and gastric emptying, regulating blood flow and permeability, regulating immune functions, and stimulating the growth of cells (within and beyond the GIT).

Examples:

- Ghrelin, secreted from the stomach, and motilin, secreted from the duodenum, send a "hungry" message to the brain, while hormones PYY 3-36, CCK, glucagon-like polypeptide-I (GLP-1), oxyntomodulin, pancreatic polypeptide, and gastrin-releasing polypeptide (bombesin) send a satiety message.

- Some of the GI hormones, including some of those that affect satiety, also tend to slow gastric emptying and decrease secretions (e.g. somatostatin), while other GI hormones (e.g., motilin) increase motility.

The signaling agents of the GIT are also involved in several metabolic functions.

For instance, the neuropeptides glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 are called incretin hormones because they help lower blood sugar by facilitating insulin secretion, decreasing gastric emptying, and increasing satiety.

Several of these neuropeptide hormones and analogs are used in management of obesity, inflammatory bowel disease, diarrhea, diabetes, GI malignancies, and other conditions.

TABLE 1-3

Functions of Major Gastrointestinal Hormones

Hormone	Site of Release	Stimulants for Release	Organ Affected	Effect on Organ
Gastrin	Gastric mucosa, duodenum	Peptides, amino acids, caffeine Distention of the antrum Some alcoholic beverages, vagus nerve	Stomach, esophagus, GIT in general	Stimulates secretion of HCl and pepsinogen. Increases gastric antral motility. Increases lower esophageal sphincter tone.
			Gallbladder	Weakly stimulates contraction of gallbladder.
			Pancreas	Weakly stimulates pancreatic secretion of bicarbonate.
Secretin	Duodenal mucosa	Acid in small intestine	Pancreas	Increases output of H_2O and bicarbonate; increases some enzyme secretion from the pancreas and insulin release.
			Duodenum	Decreases motility. Increases mucus output.
CCK	Proximal small bowel	Peptides, amino acids, fats, HCl	Pancreas	Stimulates secretion of pancreatic enzymes.
			Gallbladder	Causes contraction of gallbladder.
			Stomach	Slows gastric emptying.
			Colon	Increases motility. May mediate feeding behavior.
GIP	Small intestine	Glucose, fat	Stomach, pancreas	Stimulates insulin release.
GLP-1	Small intestine	Glucose, fat	Stomach, pancreas	Prolongs gastric emptying Inhibits glucagon release. Stimulates insulin release.
Motilin	Stomach, small and large bowel	Biliary and pancreatic secretions	Stomach, small bowel, colon	Promotes gastric emptying and GI motility.

TABLE 42.1 GASTROINTESTINAL HORMONES

PEPTIDE	ACTION	SITE OF RELEASE	STIMULANT
Endocrine			
Gastrin	Stimulates: Gastric acid secretion Histamine release Growth of gastric oxyntic gland mucosa Inhibits apoptosis Inhibits somatostatin	Antrum (duodenum)	Peptides Amino acids Distention Vagal stimulation GRP, PACAP, NPY
CCK	Stimulates: Gallbladder contraction Pancreatic enzyme secretion Somatostatin secretion Pancreatic bicarbonate secretion Growth of exocrine pancreas Inhibits gastric emptying Inhibits gastric acid production Appetite suppressant	Duodenum Jejunum	Peptides Amino acids Fatty acids >8 C in length, monitor peptide, diazepam-binding inhibitor, CCK-releasing peptide
Secretin	Stimulates: Pancreatic bicarbonate secretion Biliary bicarbonate secretion Somatostatin secretion Growth of exocrine pancreas Pepsin secretion Inhibits: Gastric acid secretion Trophic effect of gastrin	Duodenum	Acid Pancreatic phospholipase A_2 Possibly bile and fatty acids
GIP	Stimulates insulin release Inhibits gastric acid secretion Inhibits gastric acid secretion	Duodenum Jejunum	Glucose Amino acids Fatty acids

TABLE 42.1 GASTROINTESTINAL HORMONES

PEPTIDE	ACTION	SITE OF RELEASE	STIMULANT
Endocrine			
Peptide YY	Ileal brake Appetite suppressant May inhibit pancreatic secretion	Ileum Colon	Fatty acids Glucose
Motilin	Stimulates gastric and duodenal motility	Duodenum Jejunum	Ach, 5-HT_3
Oxyntomodulin	Inhibit gastric emptying Inhibit exocrine pancreatic secretions Appetite suppressant	Ileum Colon	Carbohydrate, protein, fat
Pancreatic polypeptide[a]	Inhibits: Pancreatic bicarbonate secretion Pancreatic enzyme secretion Gastric motility Appetite suppressant	Pancreas Colon	Protein Vagal stimulation
Enteroglucagon[a]	Inhibits gastric emptying	Ileum	Glucose Fat
Amylin (islet amyloid polypeptide)	Inhibit gastric emptying Inhibit glucagon secretion Appetite suppressant	Pancreas	Nutrient ingestion

TABLE 42.1 GASTROINTESTINAL HORMONES

PEPTIDE	ACTION	SITE OF RELEASE	STIMULANT
Neurocrine			
VIP	Relaxes sphincters Relaxes gut circular muscle Stimulates intestinal secretion Stimulates pancreatic secretion Stimulate somatostatin release	Mucosa and smooth muscle of GI tract	Released from neurons and immune cells
GRP (bombesin)	Stimulates gastrin release Stimulates somatostatin release May stimulate exocrine pancreatic secretions	Gastric mucosa	Nutrient ingestion
Substance P	Mediates pain reflexes	Spinal afferent neurons	Afferent nerve input
Enkephalins, endomorphins, dynorphins	Stimulates smooth muscle contraction Inhibits intestinal secretion	Mucosa and smooth muscle of GI tract	Unknown,? Trpm5 cation channel

TABLE 42.1 GASTROINTESTINAL HORMONES

PEPTIDE	ACTION	SITE OF RELEASE	STIMULANT
Paracrine			
Somatostatin	Inhibits: Gastrin release Other peptide hormone release Gastric acid secretion Exocrine pancreatic secretions	Gastric antrum and fundus Pancreatic islets	Acid Gastrin, GRP, VIP, PACAP, secretin, ANP, β_2/β_3–adrenergic agonists adrenomedullin, amylin, adenosine, CGRP Vagus, histamine, and interferon-γ inhibits release,
GLP-1, GLP-2	Stimulates insulin secretion, Increase proliferation, Inhibits apoptosis Inhibits motility (ileal brake) Appetite suppressant	Small bowel	Nutrient ingestion
Insulinlike growth factor-I	Increase proliferation	Gut mucosal cells, liver	Nutrient ingestion
Histamine[b]	Stimulates gastric acid secretion	Oxyntic gland mucosa ECL cell	gastrin
Epidermal growth factor	Stimulates proliferation Stimulates pepsinogen secretion Decrease gastric acid, increase gland cells	Salivary gland	Possible damage to the mucosa (ulceration or resection)
Leptin	Regulates food intake at hypothalamus, decreases NPY release	Adipose tissue, chief cells	CCK, gastric volume, glucose, cytokines
Ghrelin	Stimulates food intake, GH release	Gastric endocrine cells in the fundus	Fasting

Ach, acetylcholine; ANP, atrial natriuretic peptide; CCK, cholecystokinin; ECL, enterochromaffinlike; CGRP, calcitonin gene-related peptide; GH, growth hormone; GI, gastrointestinal; GIP; glucose-dependent insulinotropic peptide; GLP, glucagon-like peptide; GRP, gastrin-releasing peptide; 5-HT_3, 5-hydroxytryptamine; NPY, neuropeptide Y; PACAP, pituitary adenylate–cyclase activation peptide; VIP, vasoactive intestinal polypeptide.

[a]Unknown physiologic function.
[b]Histamine is an amine, not a peptide.

Gastrin

- A hormone that **stimulates gastric secretions and motility, and is secreted primarily from endocrine "G" cells in the antral mucosa of the stomach**.

- Its secretion is initiated by:

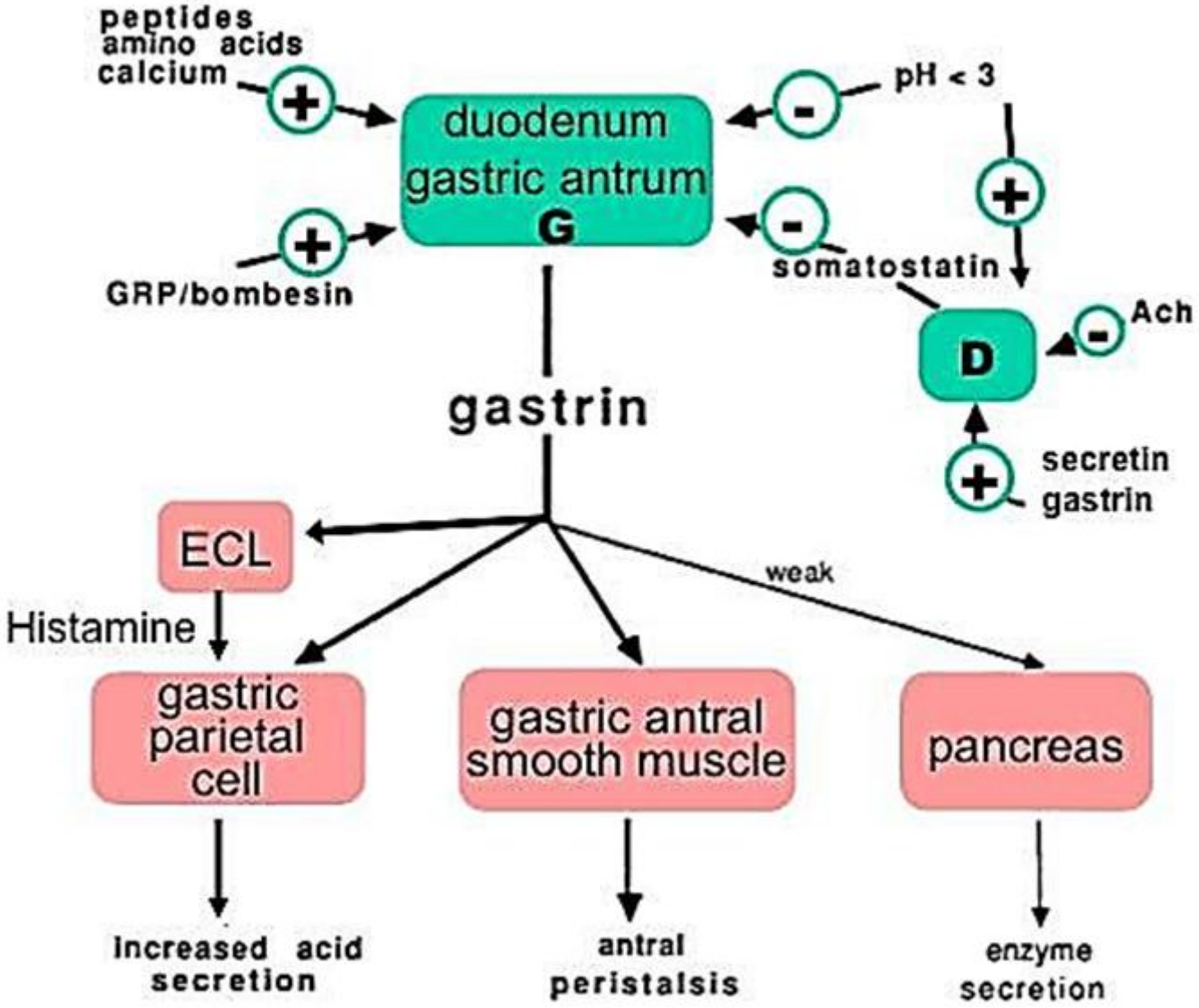
(1) Distention of the antrum after a meal
(2) Impulses from the vagus nerve such as those triggered by the smell or sight of food
(3) The presence in the antrum of secretagogues such as partially digested proteins, fermented alcoholic beverages, caffeine, or food extracts (e.g. bouillon)

When the intestinal lumen gets more acidic, feedback involving other hormones inhibits gastrin release.

Gastrin binds to receptors on:

(1) Parietal cells and histamine-releasing cells to stimulate gastric acid secretion
(2) **Chief cells to release pepsinogen**
(3) **Smooth muscle to increase gastric motility**

Gastrin summary

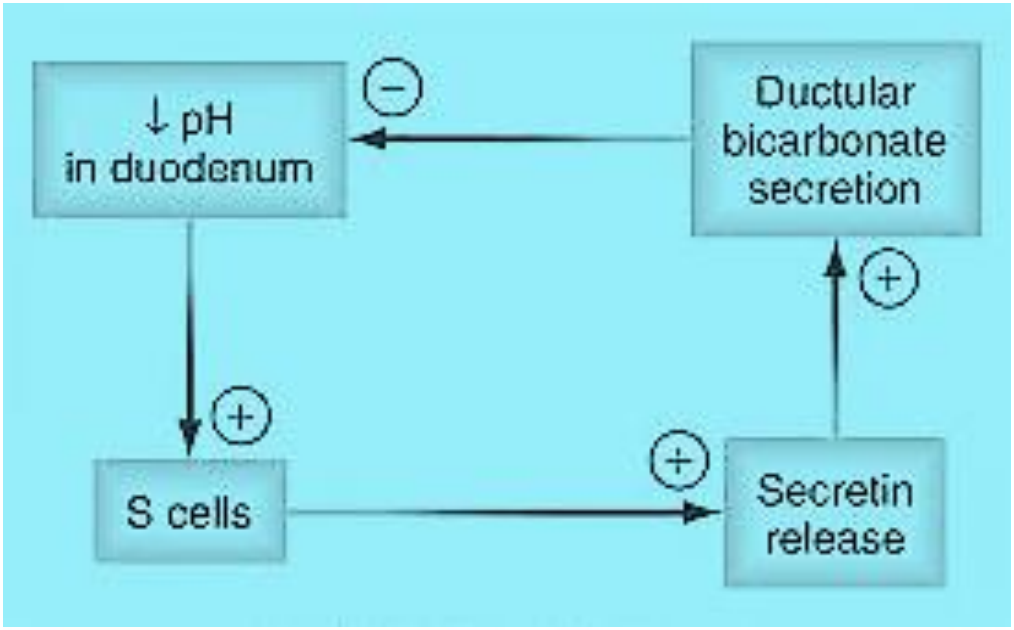


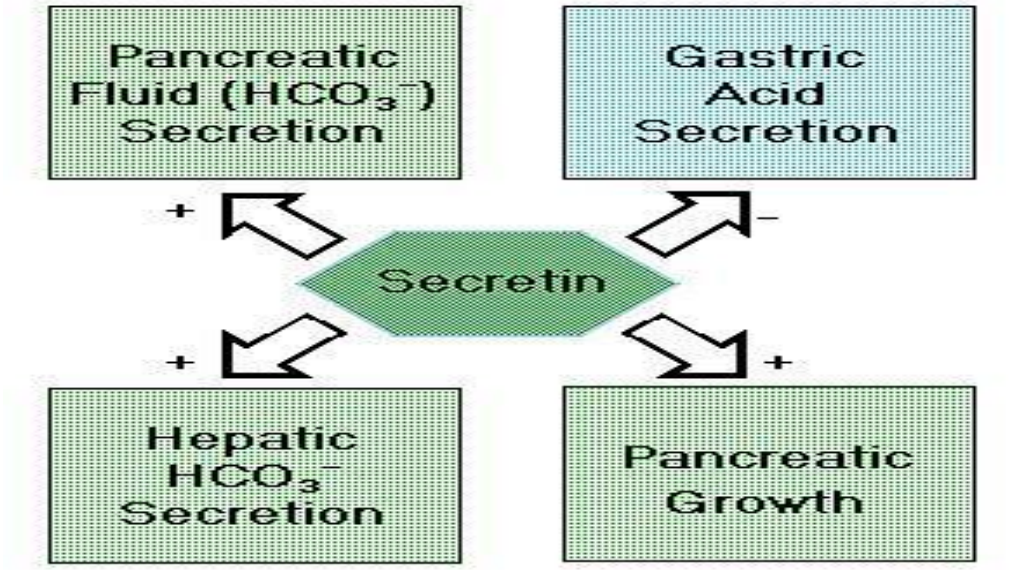
Secretin

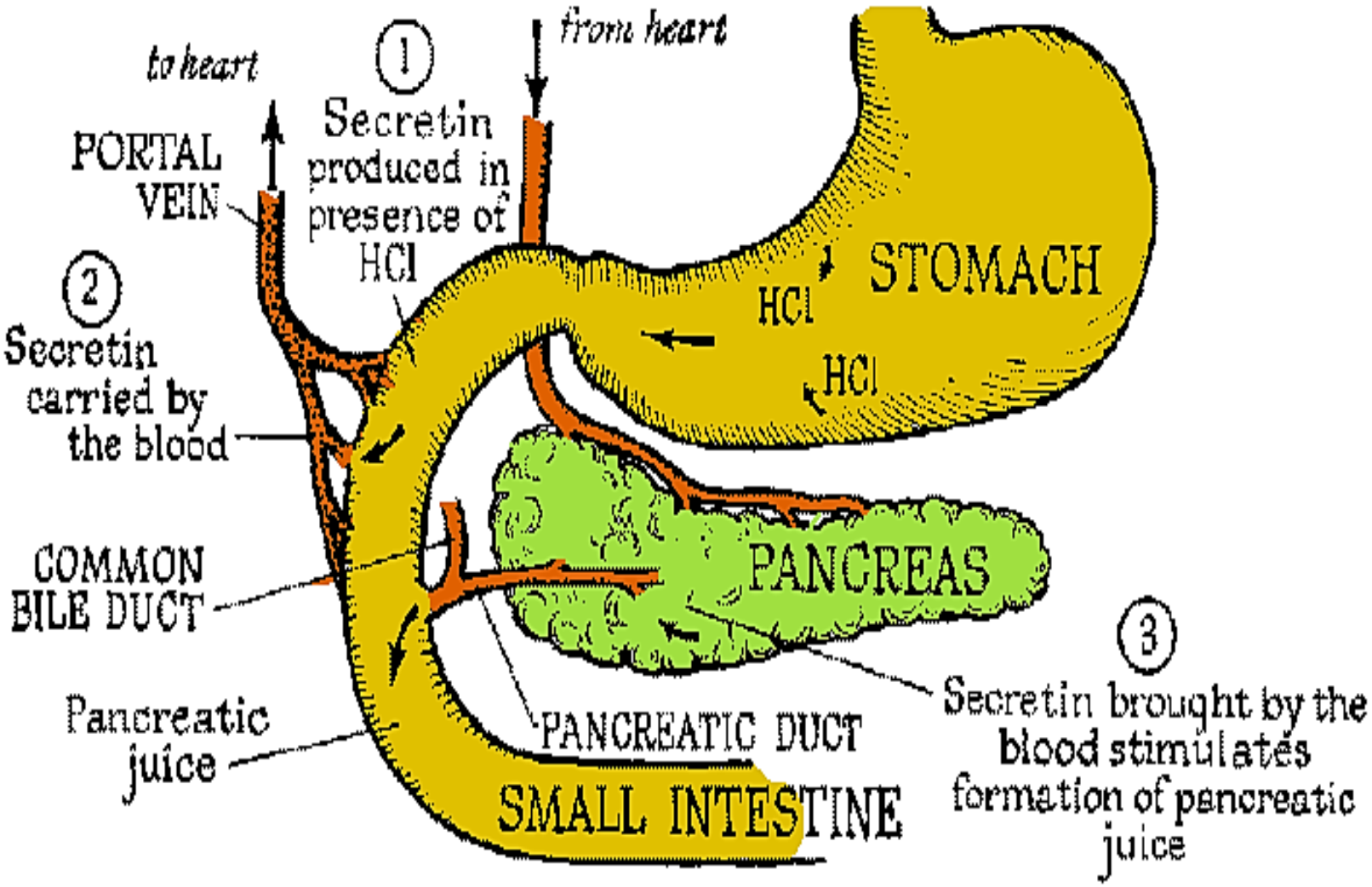
- Is the first hormone to be named.

- Is released from "S" cells in the wall of the proximal small intestine in response to the presence of gastric acid and digestive end products in the duodenum.

- Stimulates the pancreas to secrete water and bicarbonate into the duodenum, and inhibits gastric acid secretion and emptying (the opposite of gastrin).


↓ pH
in duodenum
Ductular
bicarbonate
secretion
S cells
Secretin
release


Pancreatic
Fluid (HCO_3^-)
Secretion
Gastric
Acid
Secretion
Secretin
Hepatic
HCO_3^-
Secretion
Pancreatic
Growth


to heart
from heart
1
Secretin produced in presence of HCl
PORTAL VEIN
2
Secretin carried by the blood
STOMACH
HCl
HCl
COMMON BILE DUCT
PANCREAS
3
Secretin brought by the blood stimulates formation of pancreatic juice
Pancreatic juice
PANCREATIC DUCT
SMALL INTESTINE

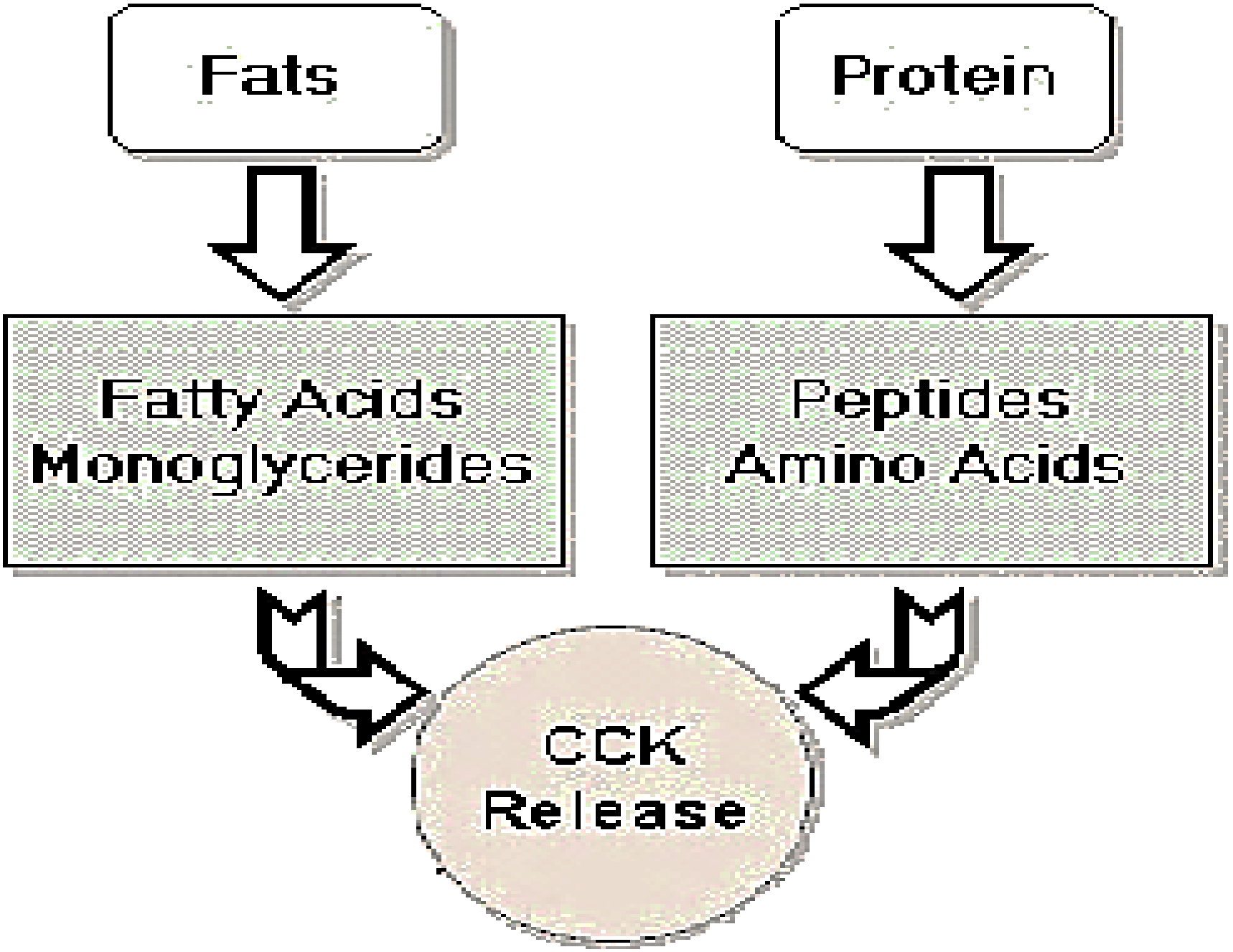
Neutralized acidity protects the duodenal mucosa from prolonged exposure to acid and provides the appropriate environment for intestinal and pancreatic enzyme activity.

The human receptor for secretin is found in the stomach and ductal and acinar cells of the pancreas.

Cholecystokinin (CCK)

- Is secreted from small bowel mucosal "I" cells in response to the presence of protein and fat.

- Its receptors are in pancreatic acinar cells, pancreatic islet cells, gastric somatostatin-releasing D cells, smooth muscle cells of the GIT, and the central nervous system.


Fats
Protein
Fatty Acids
Monoglycerides
Peptides
Amino Acids
CCK
Release

CCK:

(1) Stimulates the pancreas to secrete enzymes, some bicarbonate, and water

(2) Stimulates gallbladder contraction

(3) Increases colonic and rectal motility

(4) Slows gastric emptying

(5) Increases satiety

CCK is also widely distributed in the brain and plays a role in neuronal functioning.

* CCK has several physiologic actions occurring mainly *via* reflex vagal stimulation. CCK stimulates the CCK_1 receptors at the afferent nerve terminals and activates the medullary vagal center inducing;

*1. Pancreatic enzyme secretion;

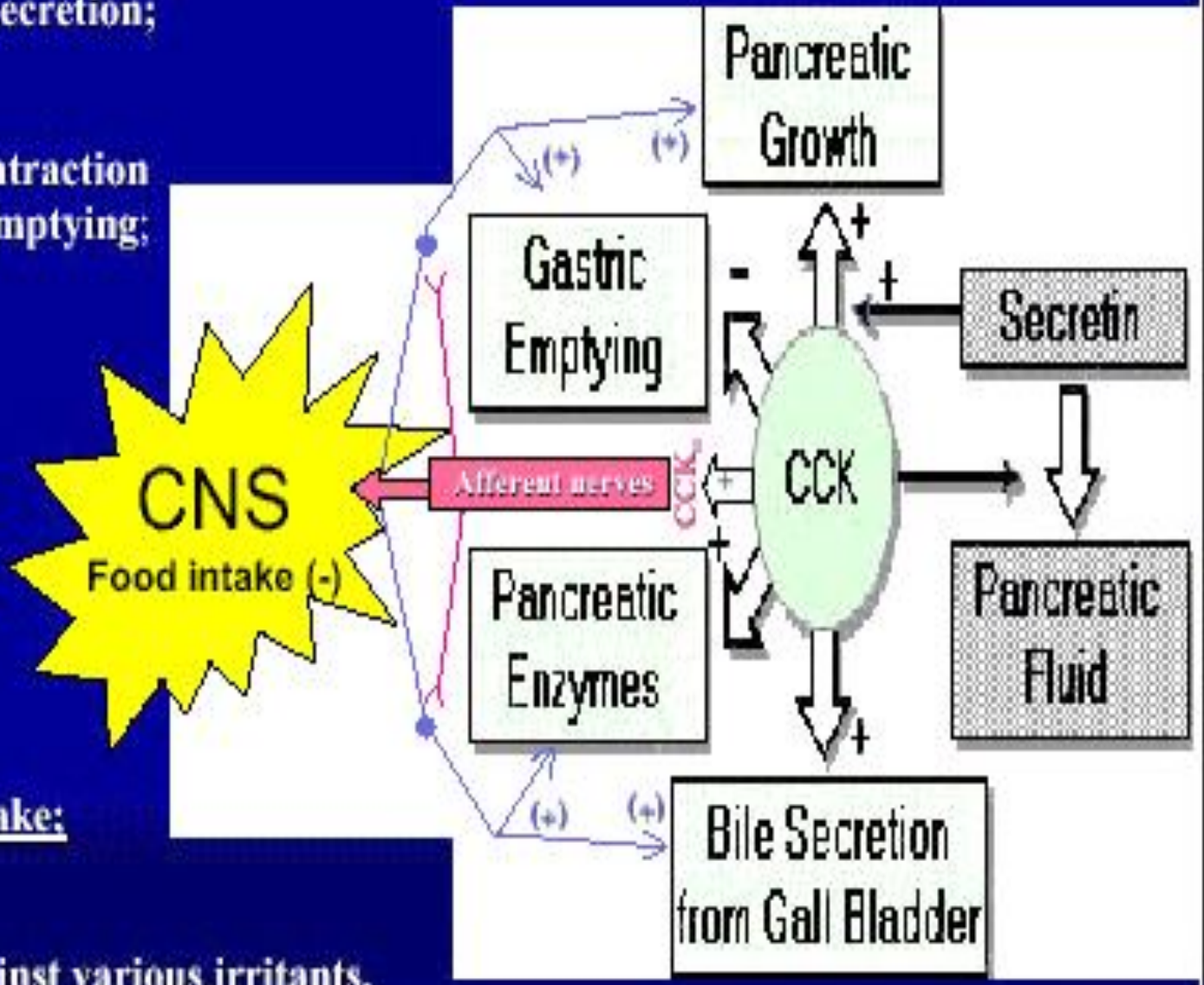
*2. Bile secretion and contraction of gall bladder and bile emptying;

*3. Inhibition of gastric emptying;

*4. Inhibition of gastric secretion;

*<u>5. Inhibition of food intake;</u>

*6. Gastroprotection against various irritants.



GLP-1 and GIP

- Are released from the intestinal mucosa in the presence of meals rich in glucose and fat, and stimulate insulin synthesis and release.

-Are examples of incretin hormones, which help keep blood glucose from rising excessively after a meal, and somehow explain why a glucose load received enterally results in less of an increase in blood glucose than when an equal amount of glucose is received intravenously.

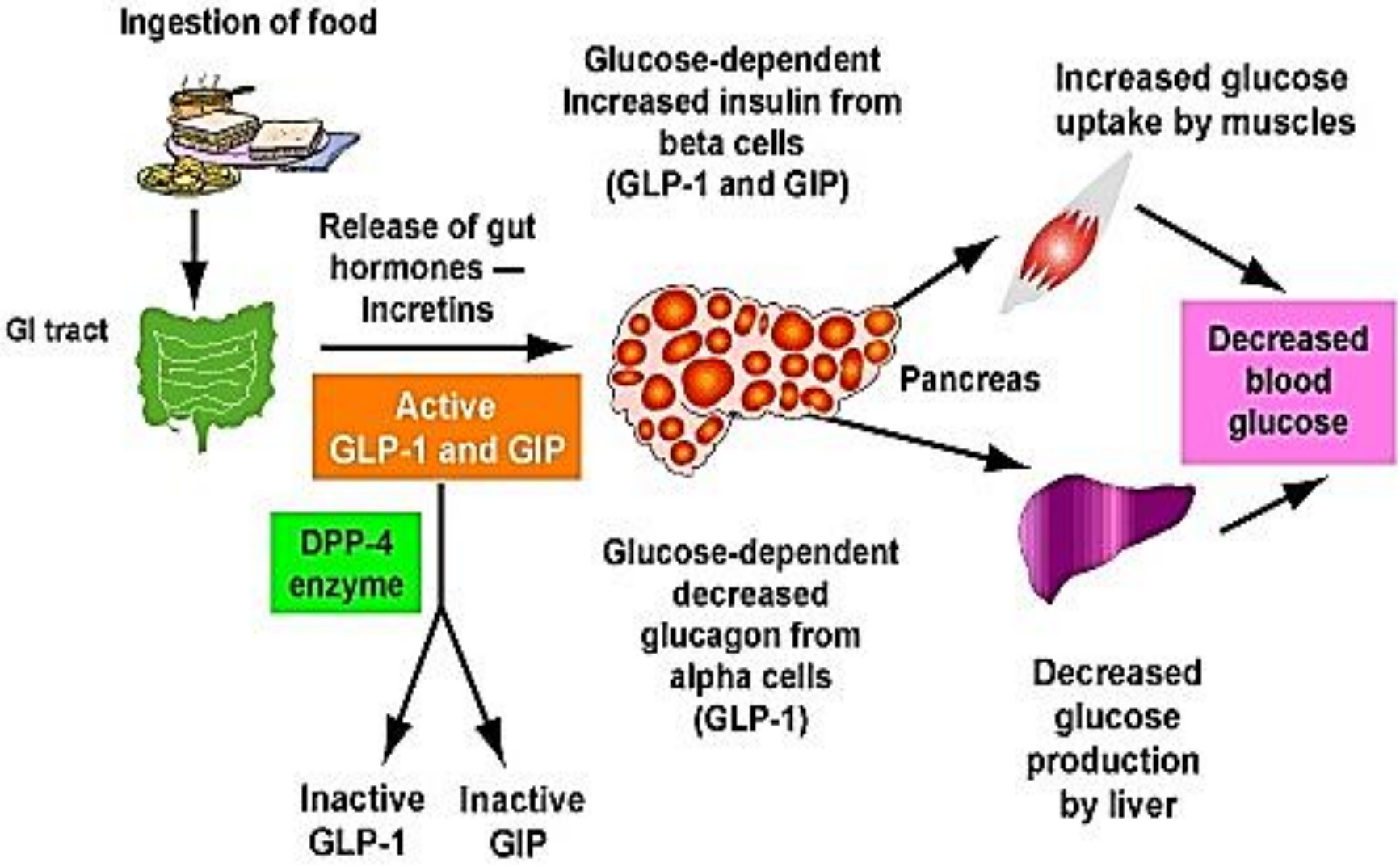
- GLP-1 also decreases glucagon secretion, delays gastric emptying, and may help promote satiety.

GLP-1 and GIP Are the 2 Major Incretins

GLP-1	GIP
• Produced by L cells mainly located in the distal gut (ileum and colon) but secreted also from proximal gut • Stimulates glucose-dependent insulin release • Suppresses hepatic glucose output by inhibiting glucagon secretion in a glucose-dependent manner • Inhibition of gastric emptying; reduction of food intake and body weight • Enhances β-cell proliferation and survival in animal models and isolated human islets	• Produced by K cells in the proximal gut • Stimulates glucose-dependent insulin release • Minimal effects on gastric emptying; no significant effects on satiety or body weight • Potentially enhances β-cell proliferation and survival in islet cell lines • Stimulates glucagon secretion

GLP, glucagon-like peptide; GIP, glucose-dependent insulinotropic polypeptide.

Role of Incretins in Glucose Homeostasis



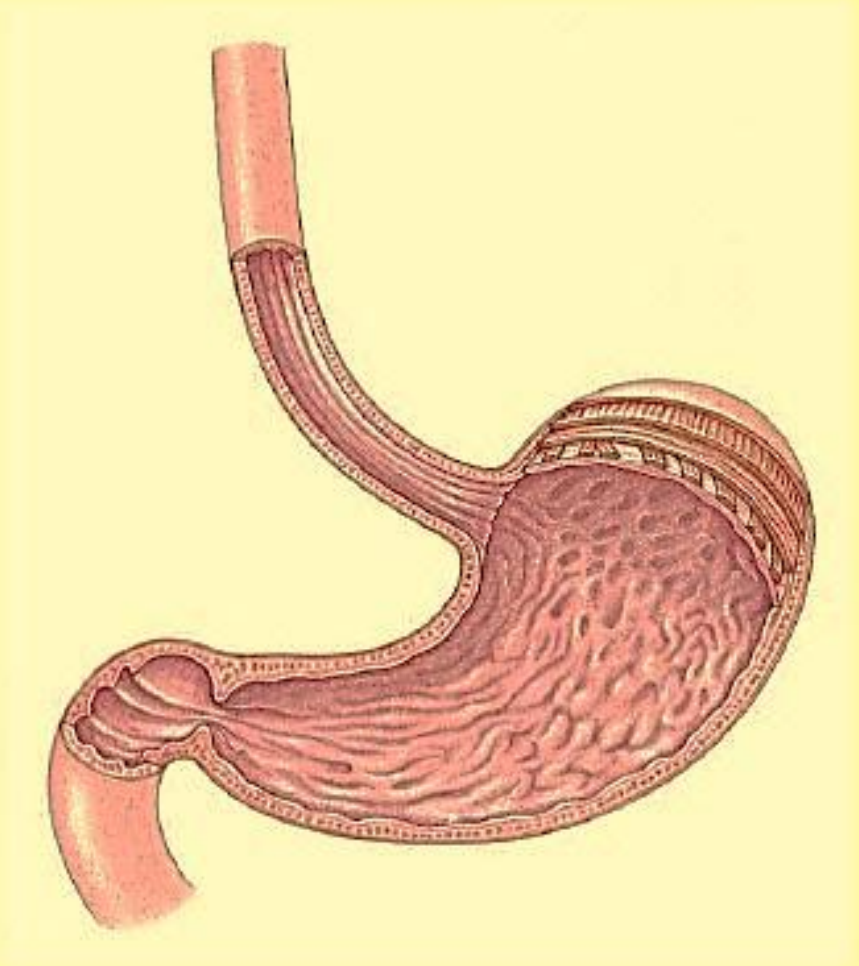
Motilin

- Is released from duodenal mucosa during fasting to stimulate GI motility (i.e. gastric emptying and intestinal movement).

- Erythromycin, an antibiotic, has been shown to bind to motilin receptors; thus analogs of erythromycin and motilin have been used as therapeutic agents to treat delayed gastric emptying.

Motilin

- It is secreted from duodenal mucosa. It has 22 amino acids.
- It is involved in movements of gut as it is found to cause contraction of smooth muscles of intestine.

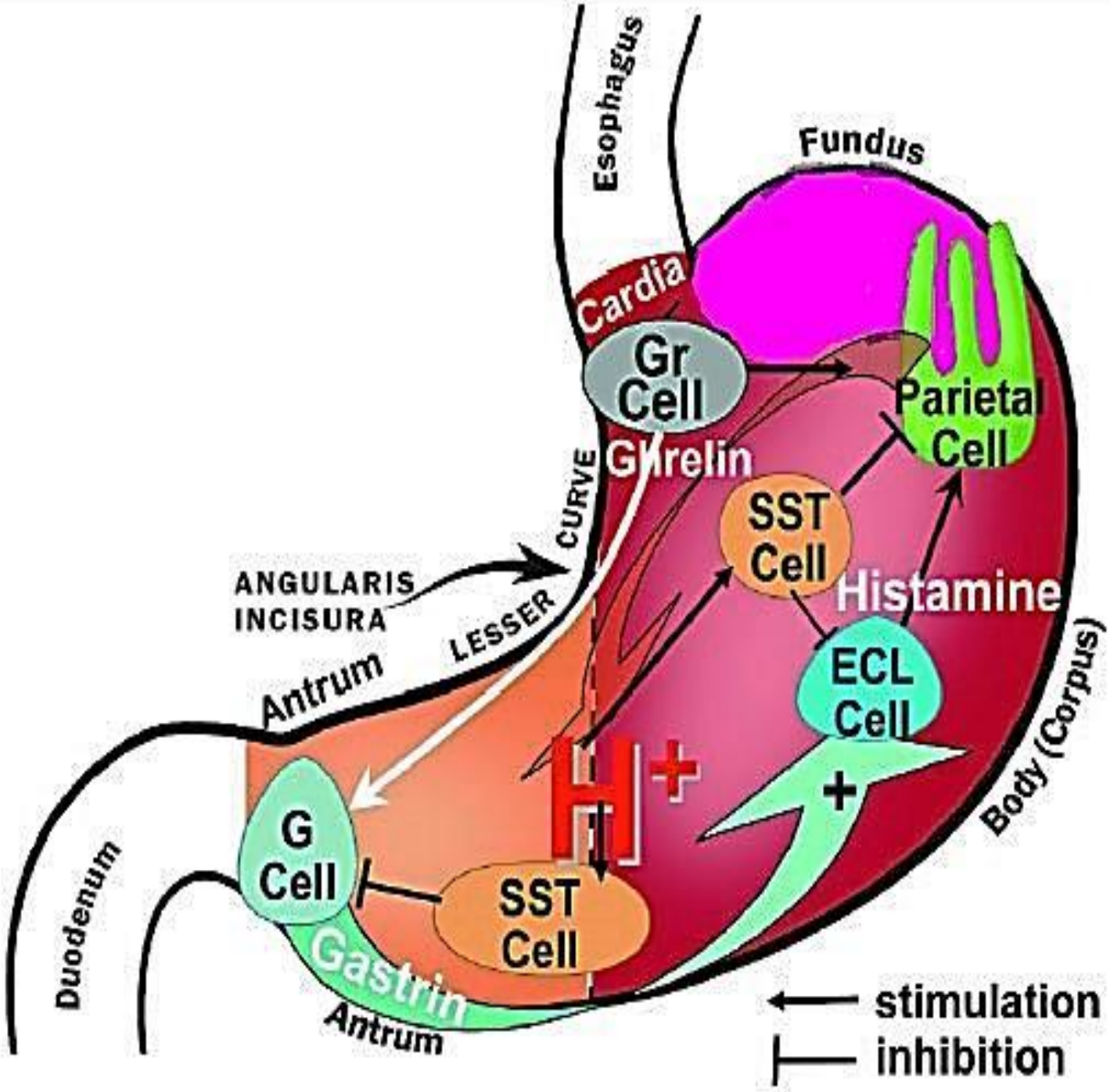


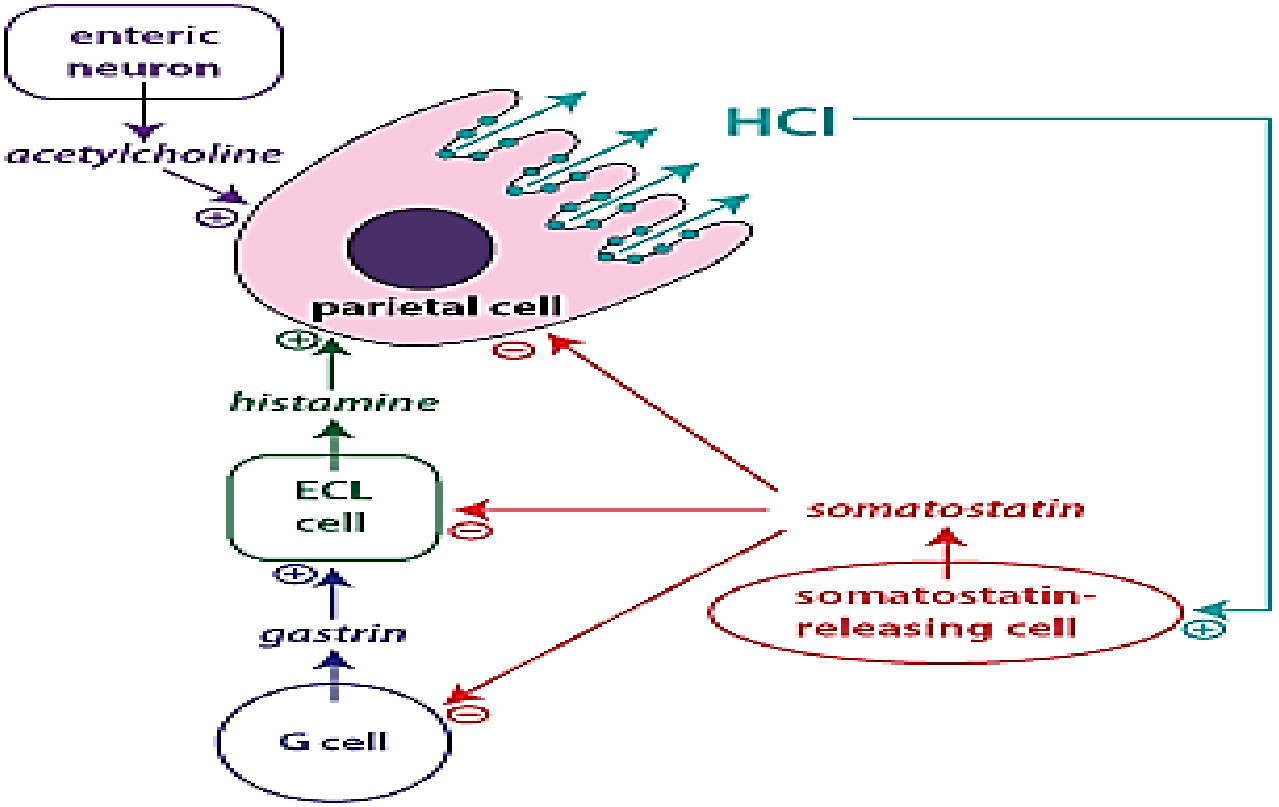
Somatostatin

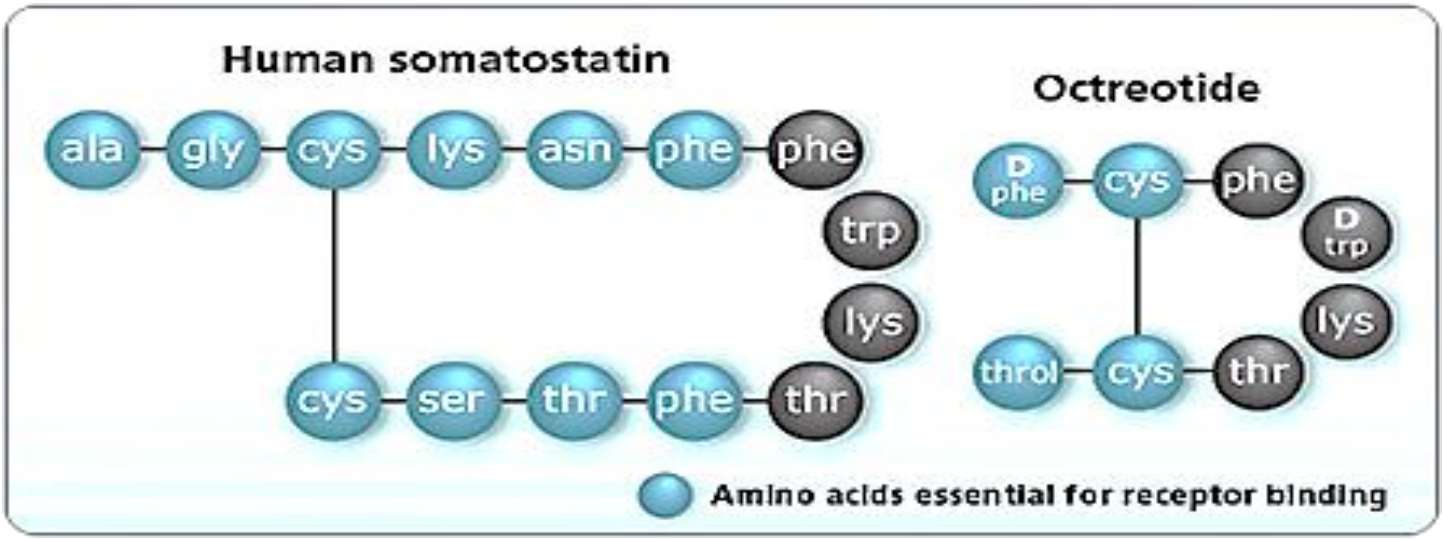
- Is released by D cells in the antrum and pylorus.

- Its primary roles are inhibitory (e.g. it decreases the motility of stomach and intestine and inhibits the release of several GI hormones).

- Somatostatin and its analog, octreotide, are being used to treat certain malignant diseases as well as numerous GI disorders such as diarrhea, short bowel syndrome, pancreatitis, dumping syndrome, and gastric hypersecretion.


Esophagus
Fundus
Cardia
Gr Cell
Ghrelin
Parietal Cell
SST Cell
Histamine
ECL Cell
CURVE
ANGULARIS INCISURA
LESSER
Antrum
H+
+
G Cell
SST Cell
Gastrin
Antrum
Duodenum
Body (Corpus)
stimulation
inhibition


enteric neuron
acetylcholine
HCl
parietal cell
histamine
ECL cell
somatostatin
somatostatin-releasing cell
gastrin
G cell


Human somatostatin
ala
gly
cys
lys
asn
phe
phe
trp
lys
cys
ser
thr
phe
thr
Octreotide
D phe
cys
phe
D trp
lys
throl
cys
thr
Amino acids essential for receptor binding

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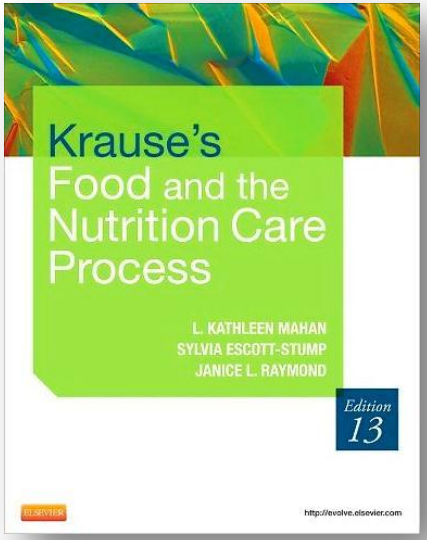
Krause's
Food and the
Nutrition Care
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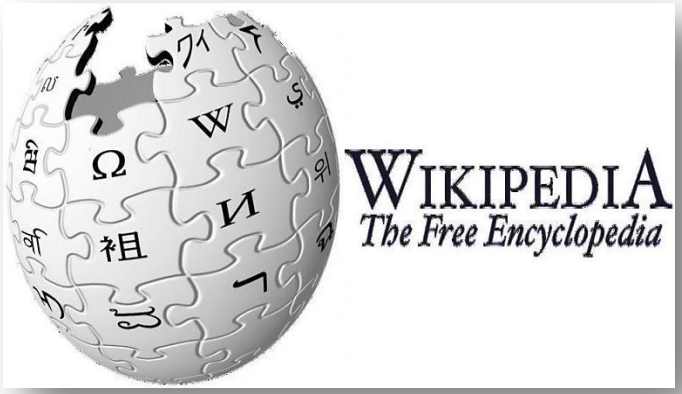
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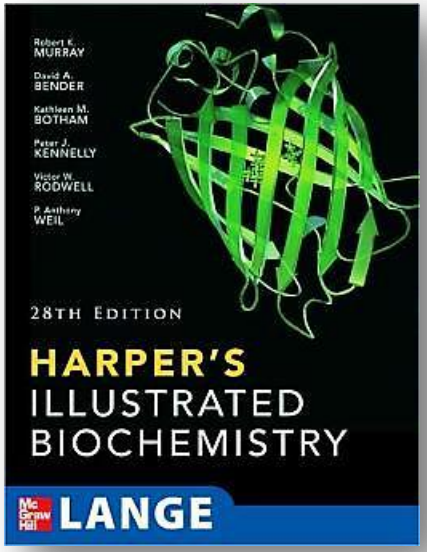
The Free Encyclopedia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Kathleen M. BOTHAM
Peter J. KENNELLY
Victor W. RODWELL
P. Anthony WEIL
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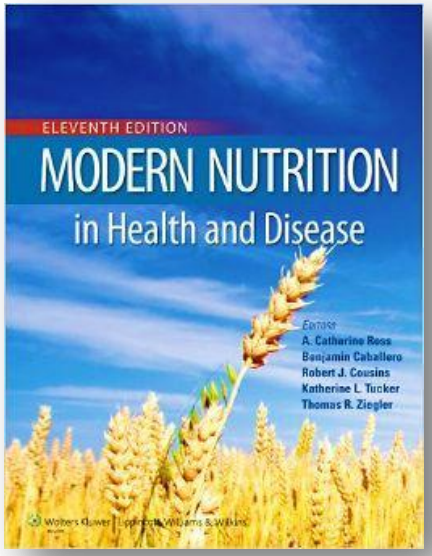
HARPER'S
ILLUSTRATED
BIOCHEMISTRY
LANGE


ELEVENTH EDITION
MODERN NUTRITION
in Health and Disease
A. Catharine Ross
Benjamin Caballero
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Thomas R. Ziegler