MEDICINE 438's

GIT PHYSIOLOGY

LECTURE IV: Physiology of the Pancreas

EDITING FILE

IMPORTANT | MALE SLIDES | EXTRA | FEMALE SLIDES | LECTURER'S NOTES

1 PHYSIOLOGY OF THE PANCREAS

Lecture Four

OBJECTIVES

- Functional Anatomy
- Major components of pancreatic juice and their physiologic roles
- Cellular mechanisms of bicarbonate secretion
- Cellular mechanisms of enzyme secretion
- Activation of pancreatic enzymes
- Hormonal & neural regulation of pancreatic secretion
- Potentiation of the secretory response

Pancreas

Lying parallel to and beneath the stomach, it is a large compound gland with most of its internal structure similar to that of the salivary glands. It is composed of:

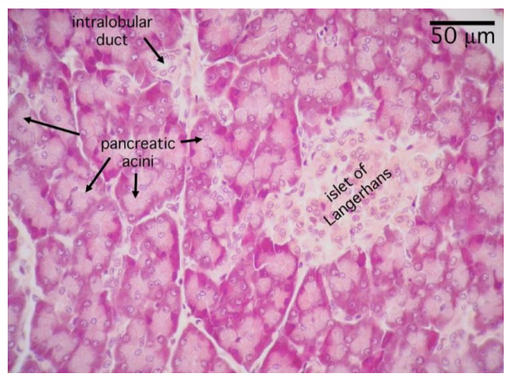

Figure 4-1

Endocrine portion 1-2%

(Made of Islets of Langerhans)

Secrete hormones into the blood

- Insulin (beta cells; 60%)
- Glucagon (alpha cells; 25%)
- Somatostatin (delta cells; 10%).

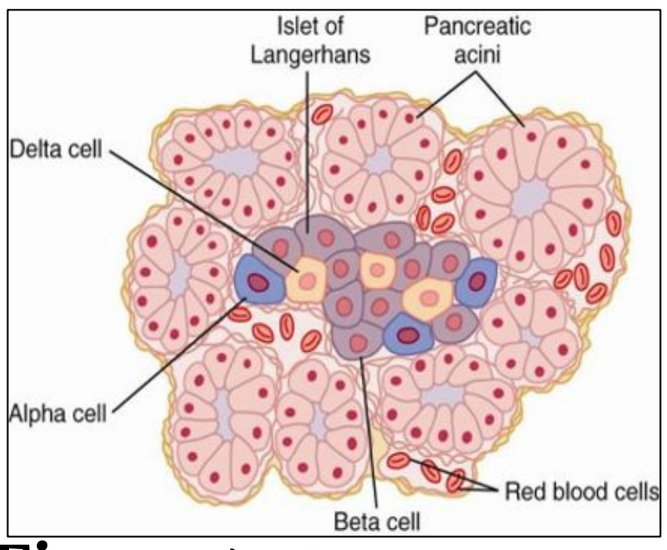

Figure 4-2

Exocrine portion 95%

(Acinar gland tissues)

Made of acinar & ductal cells.[1]

secretes digestive enzymes, HCO_3^- and water into the duodenum .

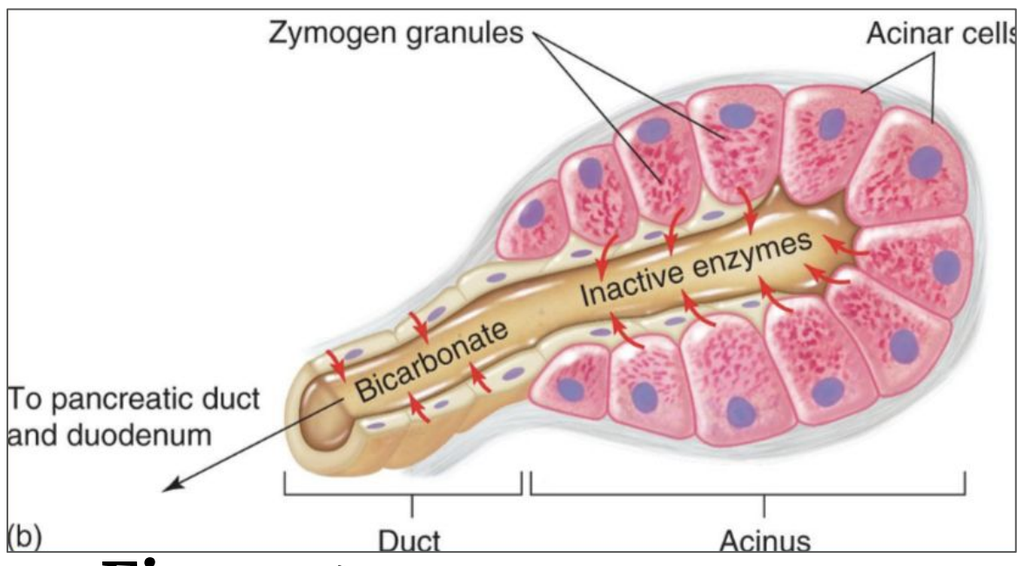

Figure 4-3

- The pancreatic digestive enzymes are secreted by **pancreatic acini.**
- Large volumes of sodium bicarbonate solution are secreted by the **small ductules** and **larger ducts** leading from the acini.
- Pancreatic juice is secreted in response to the presence of chyme in the upper portions of the small intestine.
- Insulin and Glucagon are crucial for normal regulation of glucose, lipid, and protein metabolism.

FOOTNOTES

1. Acinar cells arrange themselves like clusters of grapes, that eventually release their secretions into ducts. Collection of acinar cells is called acinus, acinus and duct constitute one exocrine gland.

Pancreatic Secretion:

- **Amount ≈ 1.5 L/day in an adult human.**
- **The major functions of pancreatic secretion:**

1. To neutralize the acids in the duodenal chyme to optimum range (pH=7.0-8.0) for activity of pancreatic enzymes.
2. To prevent damage to duodenal mucosa by acid & pepsin.
3. To produce enzymes involved in the digestion of dietary carbohydrate, fat, and protein.

Acinar Cell Secretion	Ductal Cell Secretion
• Acini provide the primary secretion in a solution with similar composition to plasma. • **Secrete** a protein-rich (digestive enzymes) proenzymes secretion in an isotonic plasma-like fluid. • Constitute 25% of total pancreatic secretion. • Stimulated by **CCK** & **Ach**	• **Secretes** a HCO_3^--rich fluid that alkalinizes & hydrates the protein-rich secretion of acinar cells. (to dilute & alkalinize the pancreatic juice) • Constitute 75% of pancreatic secretion. • Stimulated by **Secretin**. • Effects of Secretin are potentiated by **CCK** & **Ach**

Pancreatic Juice: Refers to the final combined product secreted by the exocrine pancreas.

Digestive enzymes

Proteolytic:

★ **For protein**

Trypsin, Chymotrypsin, Carboxypolypeptidase

Amylolytic:

★ **For lipids:**

Pancreatic lipase, Cholesterol Esterase, Phospholipase A2

★ **For carbohydrates:**

pancreatic Amylase

An electrolyte solution rich in HCO3-

Nucleolytic:

★ **For DNA & RNA:**

Nucleases, Ribonuclease, Deoxyribonuclease

Flow of Pancreatic Secretion into Duodenum:

01 The combined product of enzymes and $NaHCO_3$ flows through a long pancreatic duct.

02 Pancreatic duct joins the common bile duct immediately before it empties into the duodenum through the papilla of Vater, surrounded by the sphincter of Oddi.

Pancreatic enzymes for digesting proteins are:

Trypsin (active form of **Trypsinogen**)

Chymotrypsin (active form of **Chymotrypsinogen**)

Carboxypolypeptidase (active form of **Procarboxypolypeptidase**)

Trypsin and Chymotrypsin split whole and partially digested proteins into peptides of various sizes but do not cause release of individual amino acids.

Carboxypolypeptidase splits some peptides into individual amino acids, thus completing digestion of some proteins to amino acids.

These enzymes become activated only after they are secreted into the Intestinal Tract.

Trypsinogen is activated by:

- Enteropeptidase (**enterokinase**), an enzyme secreted by the intestinal mucosa when chyme comes in contact with the mucosa.
- Trypsinogen can be autocatalytically activated by trypsin formed from previously secreted trypsinogen.

Chymotrypsinogen and Procarboxypolypeptidase:

- They are activated by trypsin to form chymotrypsin and carboxypolypeptidase.

Trypsin Inhibitor:

- Secretion of trypsin inhibitor prevents digestion of the pancreas itself.
- Proteolytic enzymes of the pancreatic juice do not become activated until after they have been secreted into the intestine because the trypsin and the other enzymes would digest the pancreas itself.
- The same cells that secrete proteolytic enzymes into the acini of the pancreas secrete another substance called **trypsin inhibitor**.
- Trypsin inhibitor is formed in the cytoplasm of the glandular cells, and it prevents activation of trypsin both inside the secretory cells and in the acini and ducts of the pancreas.
- Because trypsin activates the other pancreatic proteolytic enzymes, therefore trypsin inhibitor prevents activation of the other enzymes as well.

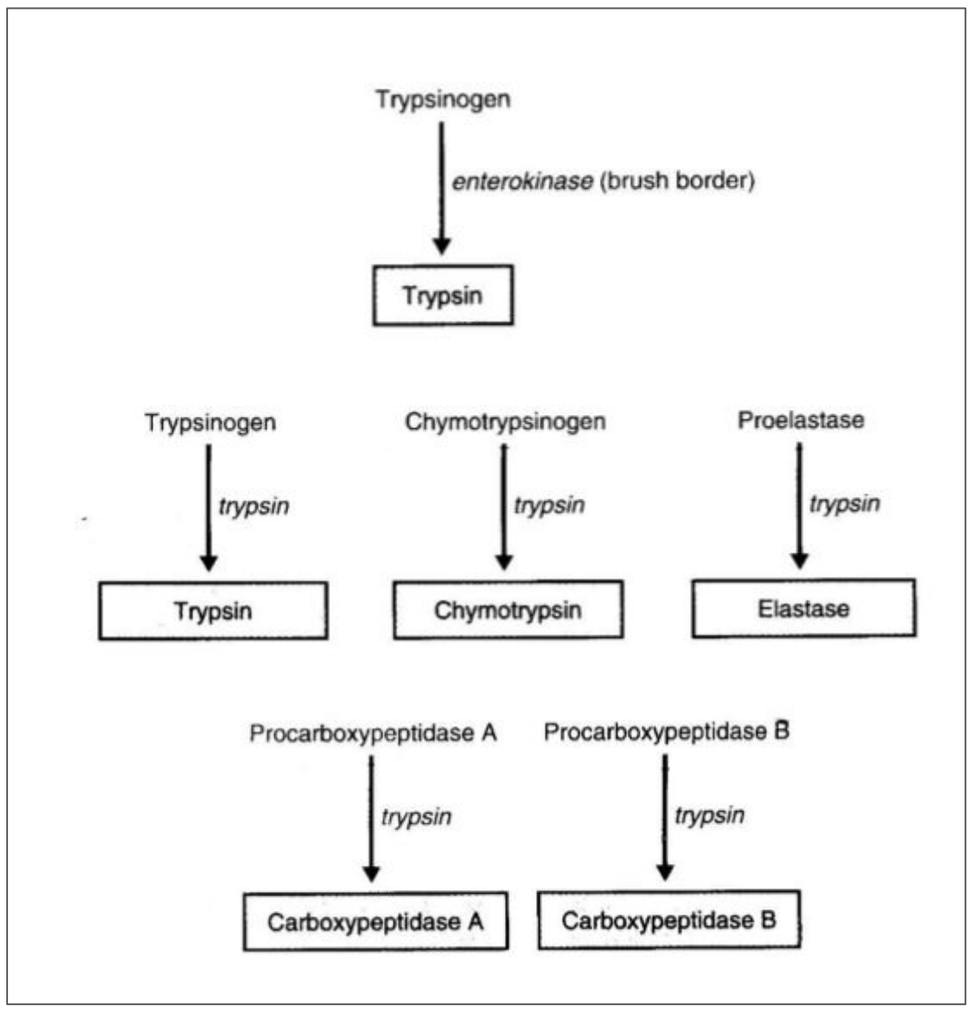

Figure 4-4 Activation of digestive enzymes in small intestine

Enzymes For Digesting Carbohydrate:

- **Pancreatic amylase**: it hydrolyzes starches, glycogen, and most other carbohydrates (except cellulose) to form mostly disaccharides and a few tri-saccharides.

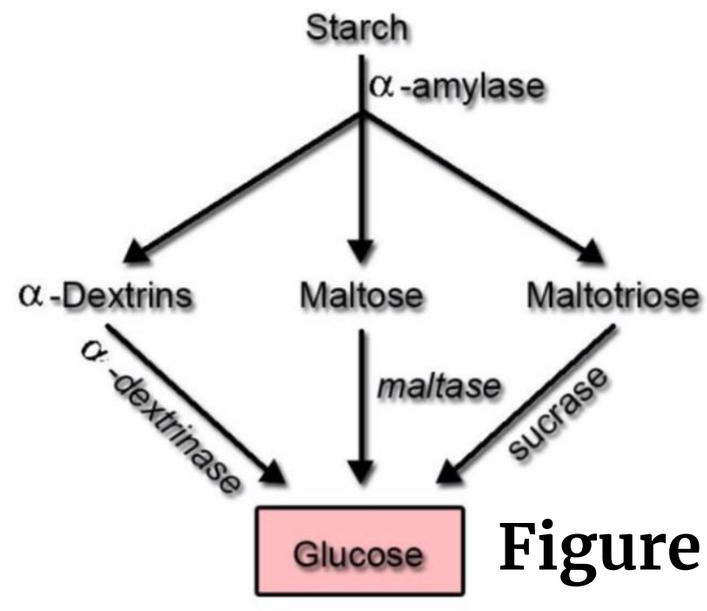

Figure 4-5

Enzymes For Digesting Fat:

(1) Pancreatic lipase (2) Cholesterol esterase (3) Phospholipase

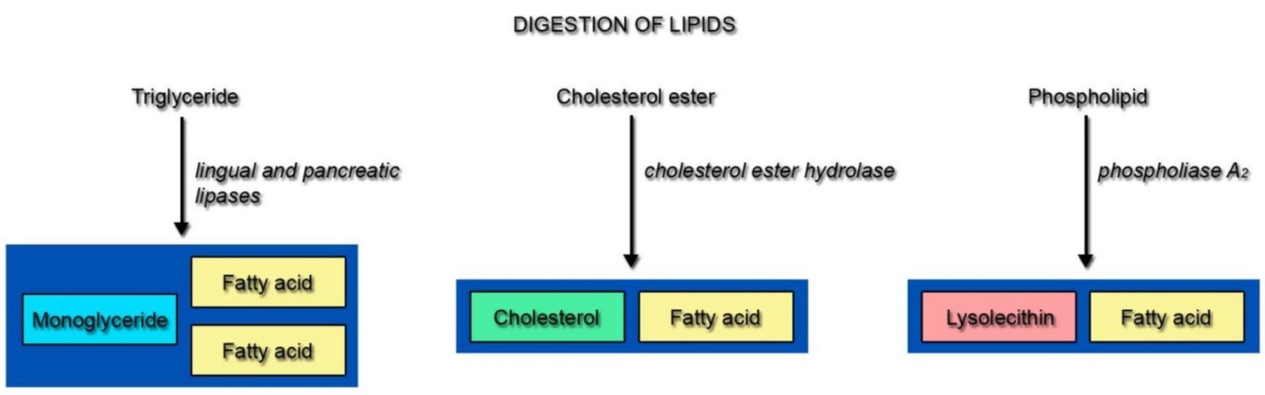

Figure 4-6

Pancreatic Secretions

- The pancreas secrets about 1 L/day of HCO_3^- rich fluid from the epithelial cells of the ductules and ducts.
- HCO_3^- is exchanged for Cl^-. Secretin increases the rate of this exchanger.
- The osmolarity of pancreatic fluid is equal to that of plasma.
- HCO_3^- concentration increases with increasing secretion rate.

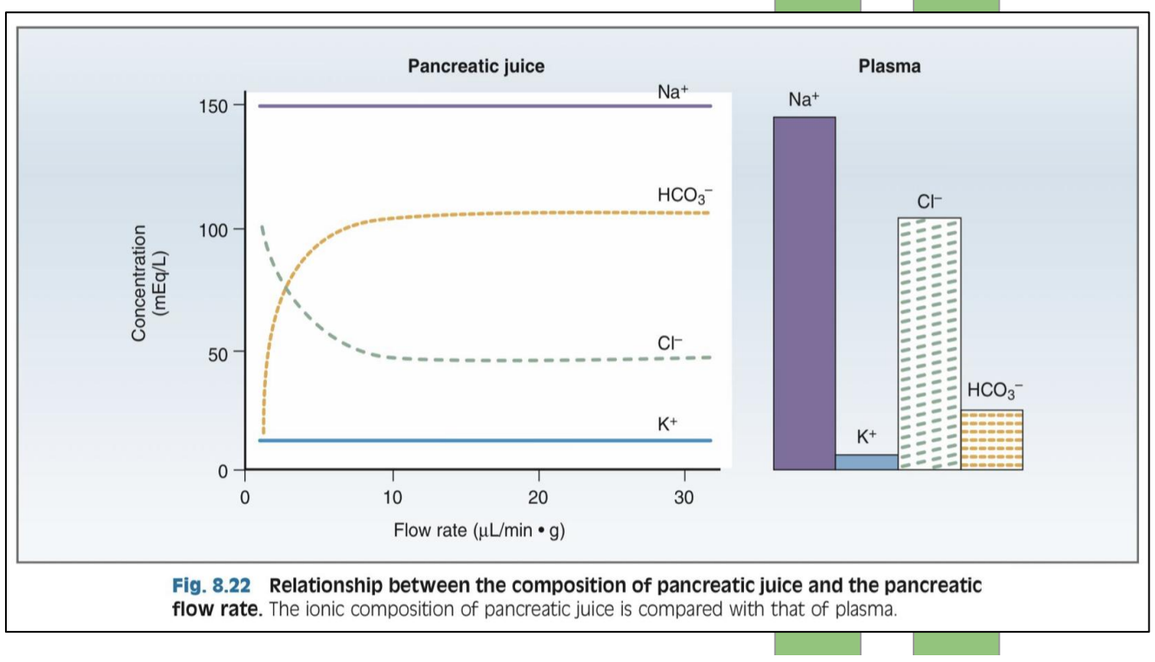

Fig. 8.22 **Relationship between the composition of pancreatic juice and the pancreatic flow rate.** The ionic composition of pancreatic juice is compared with that of plasma.

Figure 4-7, Flow Rate & Pancreatic Secretion

Mechanism of HCO_3^- Secretion:

01 Basolateral membrane contains Na^+-K^+ ATPase and a Na^+-H^+ exchanger. By this step, H^+ goes to the blood and combines with HCO_3^- which results in CO_2 & H_2O formation.

02 CO_2 and H_2O combine in ductal cells to form H_2CO_3.

03 H_2CO_3 dissociates into H^+ and HCO_3^-.

04 H^+ is transported into blood by Na^+-H^+ exchanger at basolateral membrane of ductal cells.

05 HCO_3^- is secreted into pancreatic juice by Cl^--HCO_3 exchanger at apical membrane of ductal cells, followed by osmotic flow of water. [1]

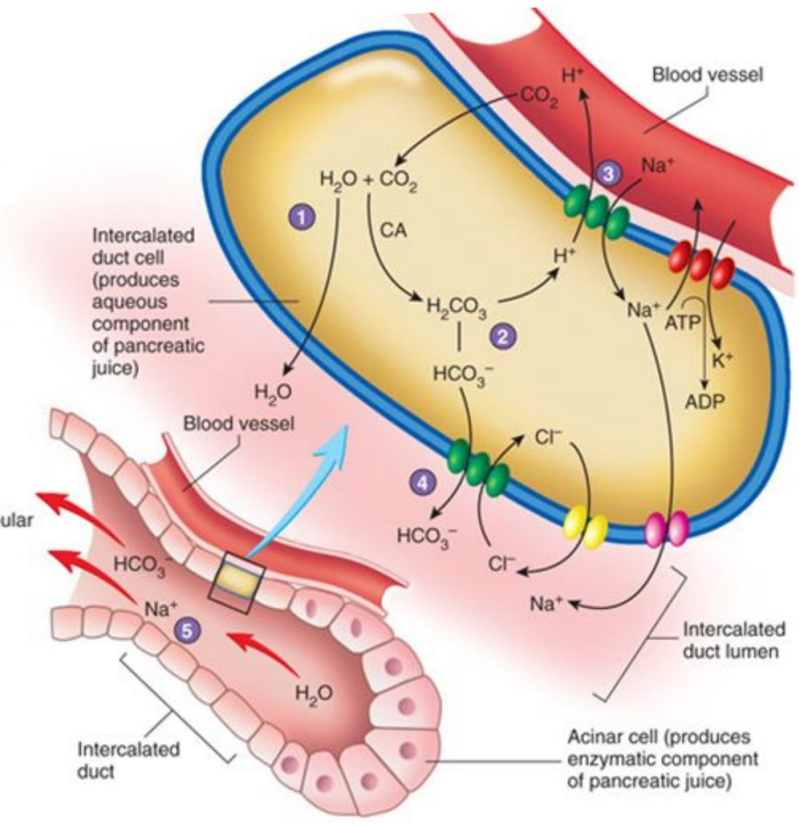

Figure 4-8

- Absorption of H^+ causes **acidification** of pancreatic venous blood.[2]

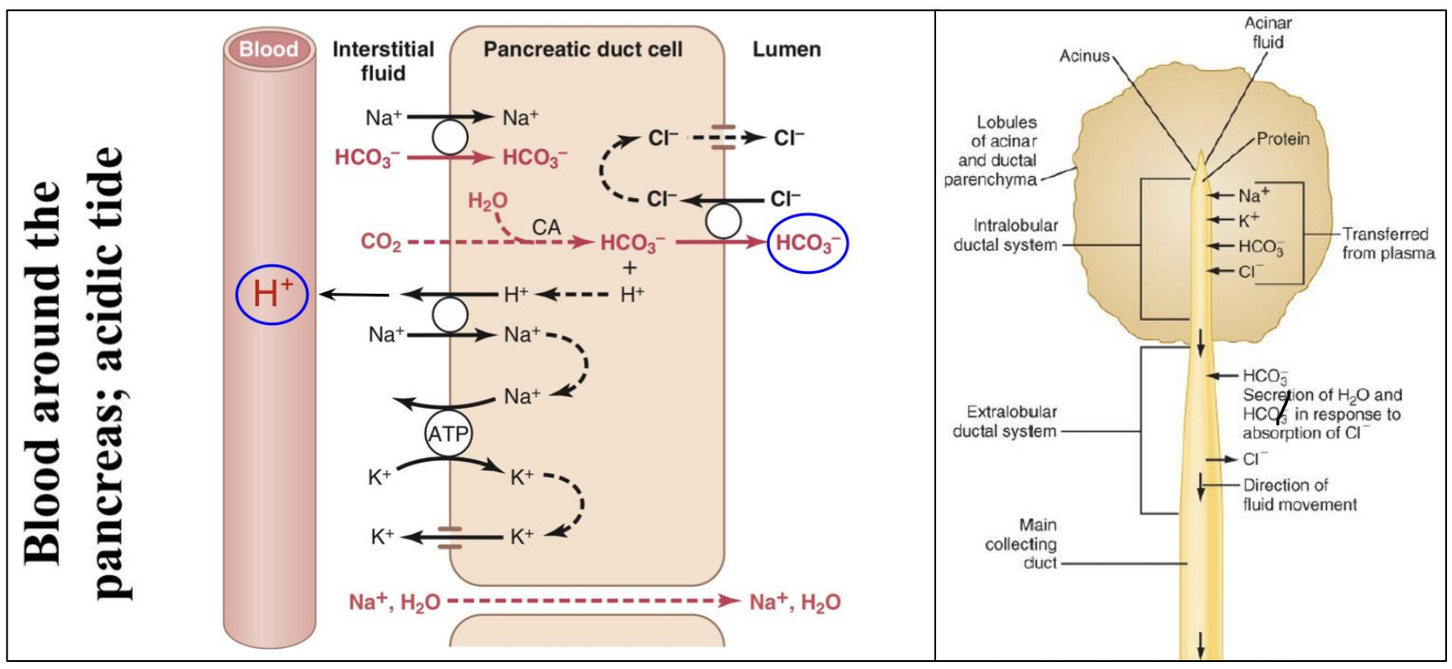

Figure 4-9

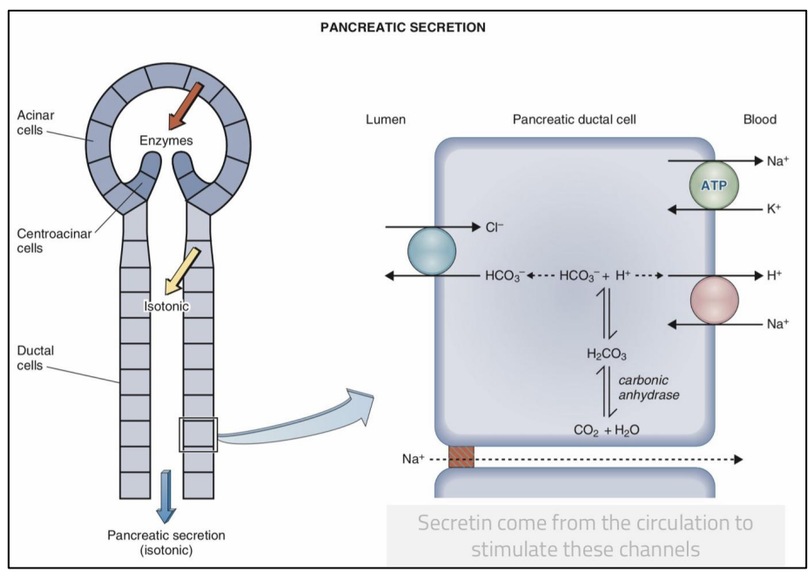

Figure 4-10, Secretion of Isosmotic Sodium Bicarbonate Solution

FOOTNOTES

1. This is a crucial step, and why **cystic fibrosis** causes pancreatitis. Failure of Cl^- secretion by the channel (CFTR) seen in Figure 4-9 results in dysfunctional activity of Cl-HCO_3^- exchanger, since there would be no chloride to exchange with bicarbonate. Bicarbonate then will not be secreted into the lumen, consequently, water will not flow into the lumen. Water is essential for the pancreatic secretions to flow out of the pancreatic duct, without water the secretions will be thick and clogged, some proteases can get activated, and we will end up with pancreatitis.
2. Venous blood coming from pancreas is acidic, whereas venous blood coming from stomach is alkaline, it is sometimes referred to as “alkaline tide”.

Phases Of Pancreatic Secretion

- Pancreatic secretion is under neural and hormonal control.
- It normally results from the combined effects of the multiple basic stimuli which potentiate each other.

Phase	Cephalic (20%)	Gastric (5-10%)	Intestinal (70-75%)
Stimulus	Smell, taste, chewing and swallowing	Protein, gastric distention	Amino acid and fatty acids in chyme
Mediator	Through Vagus nerve	Through Vagus nerve	Through hormonal stimulation (Secretin, CCK) and enteropancreatic reflexes.[3]

Pancreatic Secretion is Under Neural and Hormonal Control:

01 Parasympathetic

Stimulation through Ach on ***acinar cells***, results in increase in enzyme secretion and HCO_3^-.

Acetylcholine:

- **Released**:

  from the **para-sympathetic vagus** nerve endings & other **cholinergic nerves** in the enteric nervous system.

02 Secretin

Tends to stimulate a HCO_3^- rich secretion by activating ***ductal cells***.

- 27 amino acid polypeptide.
- HCO_3^- concentration in pancreatic secretion = 145 mmol/L

- **Release:**

  From "**S**" cells in the mucosa of the **duodenum & jejunum** (present as in an inactive form: prosecretin).[1]

- **Stimulus:**

  Mainly **acid chyme** with pH less than 4.5-5.0 in the duodenum.

03 Cholecystokinin[2]

Stimulates a marked increase in enzyme secretion by stimulating the ***acinar cells***.

- A 33-amino acid polypeptide.
- **Release:**

  From enteroendocrine "**I**" cells in the mucosa of the **duodenum & upper jejunum**.[1]

- **Stimulus:**

  By **proteoses, peptones** (products of partial protein digestion) & **long-chain fatty acids** in the chyme.

- **Acetylcholine and cholecystokinin** stimulate the acinar cells of the pancreas, causing production of large quantities of pancreatic digestive enzymes but relatively small quantities of water and electrolytes to go with the enzymes.

- **Secretin** stimulates secretion of large quantities of H_2O & $NaHCO_3$ *solution* by the pancreatic ductal epithelium.

- **Secretin** Causes the pancreas to secrete large quantities of fluid containing a high concentration of HCO_3^- (up to 145 mEq/L = ~5X normal) but a low concentration of Cl-.

  $$HCl + NaHCO_3 \rightarrow NaCl + H_2CO_3$$ (H_2CO_3 dissociates into CO2 and H2O).

- **Cholecystokinin** effect is similar to that caused by vagal stimulation but even more pronounced, accounting for 70-80% of the total secretion of the pancreatic digestive enzymes after a meal.[3]

FOOTNOTES

1. S cells function as **pH sensors**, the mechanisms are not clear but it could involve proton-gated ion channels.
2. Cholecystokinin is released in response to also cells sensing fatty acids and peptides in the lumen (probably ligand-gated ion channels) , these cells secrete **CCK- releasing peptide**, this peptide then binds on receptors on I cells and this will cause release of CCK. It's worth noting that the pancreas itself sends a peptide to sense chyme content of the lumen, this peptide is called **monitor peptide**. Monitor peptide binds to I cells when chyme content supports CCK secretion. See further readings in our last page for illustrations.
3. Cholecystokinin actually has receptors on vagal afferents near to the site of its secretion in small intestines, CCK binds to those vagal afferents to initiate a vagovagal reflex that causes more pancreatic enzymes to be secreted by action of ACh on acinar cells. **This is called an *enteropancreatic reflex.***

Regulation of pancreatic secretion:

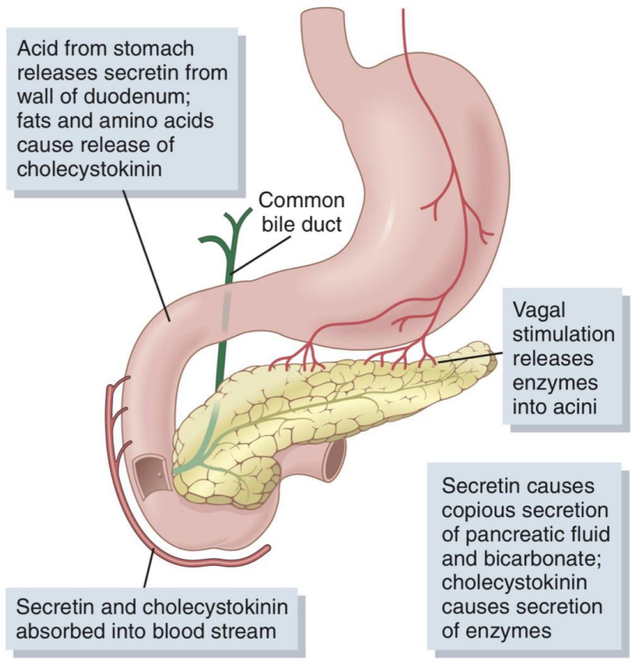

Figure 4-11

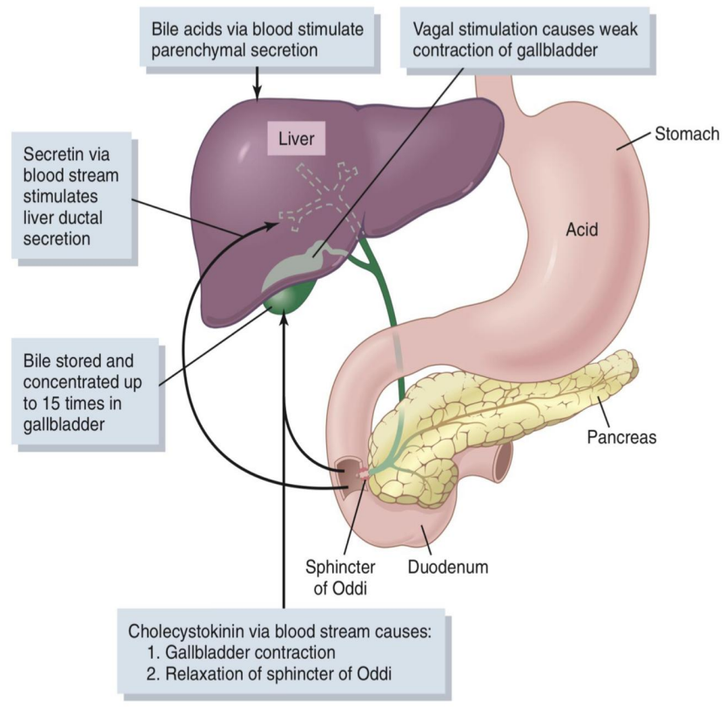

Figure 4-12

Functions Of Secretin & Cholecystokinin

Secretin

1 — Stimulates
Pancreatic secretion rich in HCO_3^- and H_2O from duct cells.

2 — Augments
stimulation of enzyme secretion by CCK.

3 — Stimulates
hepatic bile flow and HCO_3^- secretion.

4 — Inhibit
gastric acid secretion and gastrin release, but it **stimulates** pepsin secretion.

5 — Inhibit
gastric motility, contracts pylorus and slows gastric emptying, relaxes LES.

6 — Inhibit
intestinal motility and contracts ileocecal sphincter.

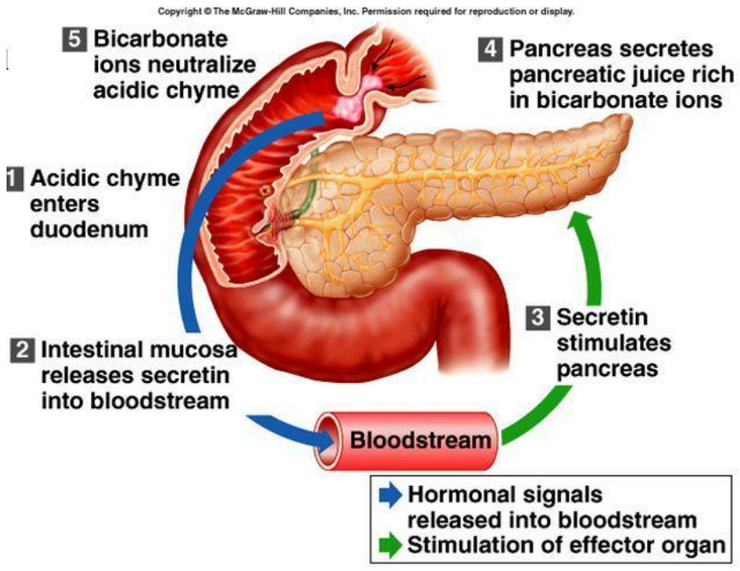

Figure 4-13

CCK

1 — Stimulates
Pancreatic enzyme secretion, accounting for 70-80% of total pancreatic digestive enzymes secretion after meal.

2 — Augments
stimulation of H_2O and HCO_3^- secretion by secretin.

3 — Stimulates
intestinal motility and relaxes ileocecal sphincter.

4 — Contract
Gallbladder, relaxes sphincter of Oddi and causes bile discharge into intestine.

5 — Has: trophic effect on pancreas. **In addition**, it may be concerned with the mechanism of satiety.

6 — Inhibits
stomach contraction moderately and slows its emptying.

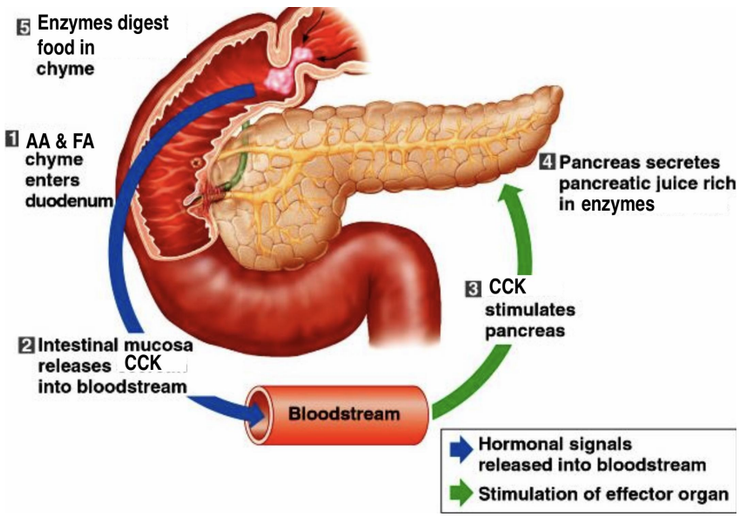

Figure 4-14

Multiplicative or Potentiation Effects of:

Different Pancreatic Secretion Stimuli

01 Usually, pancreatic secretions are the result of multiple stimuli (Ach, cholecystokinin, and secretin) rather than one stimulus alone.

02 When all these different stimuli of pancreatic secretion occur at once, then the total secretion is far greater than the sum of the secretions caused by each stimulus separately.

03 The stimuli are said to “multiply” or “potentiate” one another.

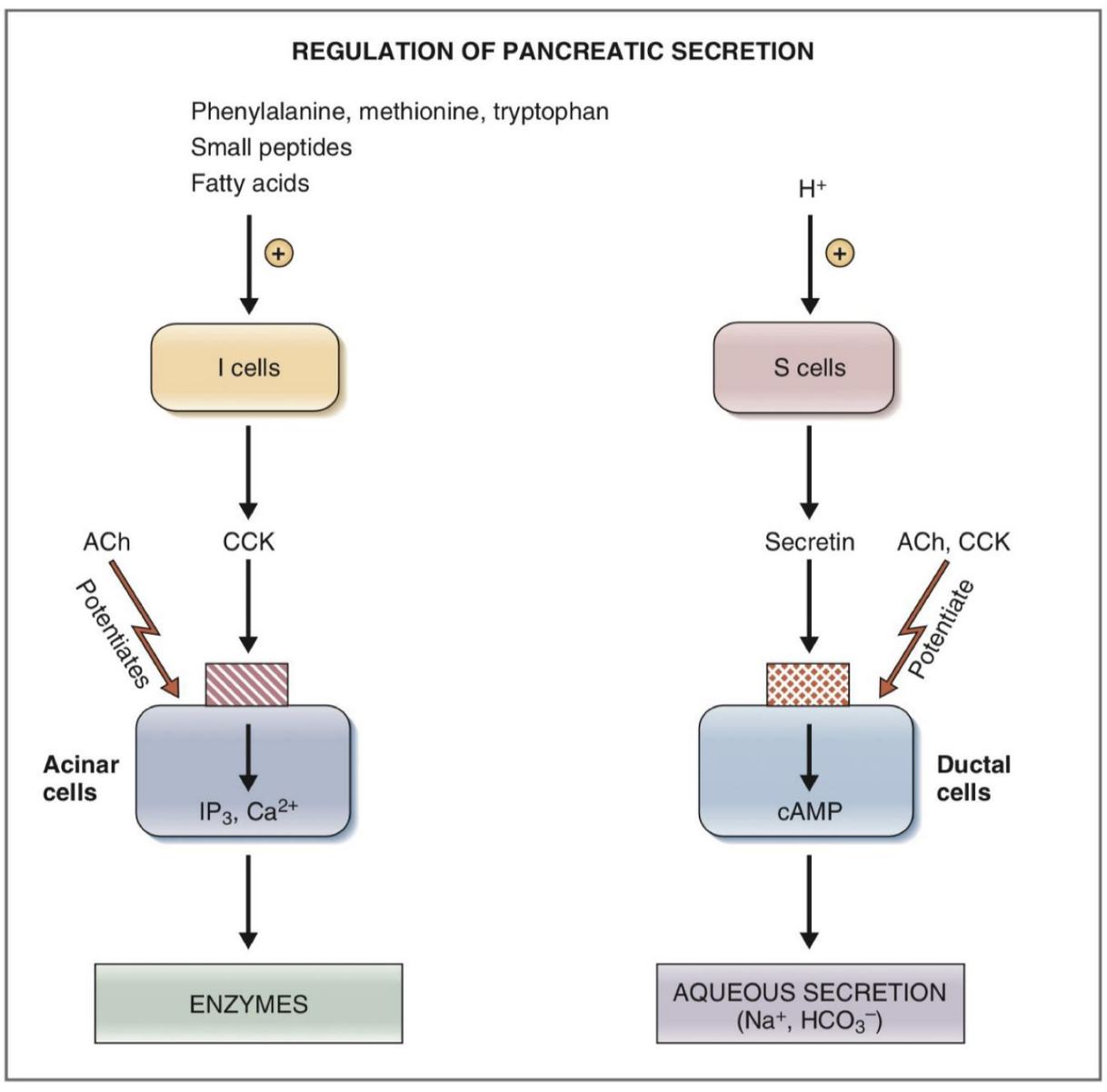

Figure 4-15

FURTHER READINGS

1. **CCK secretion**

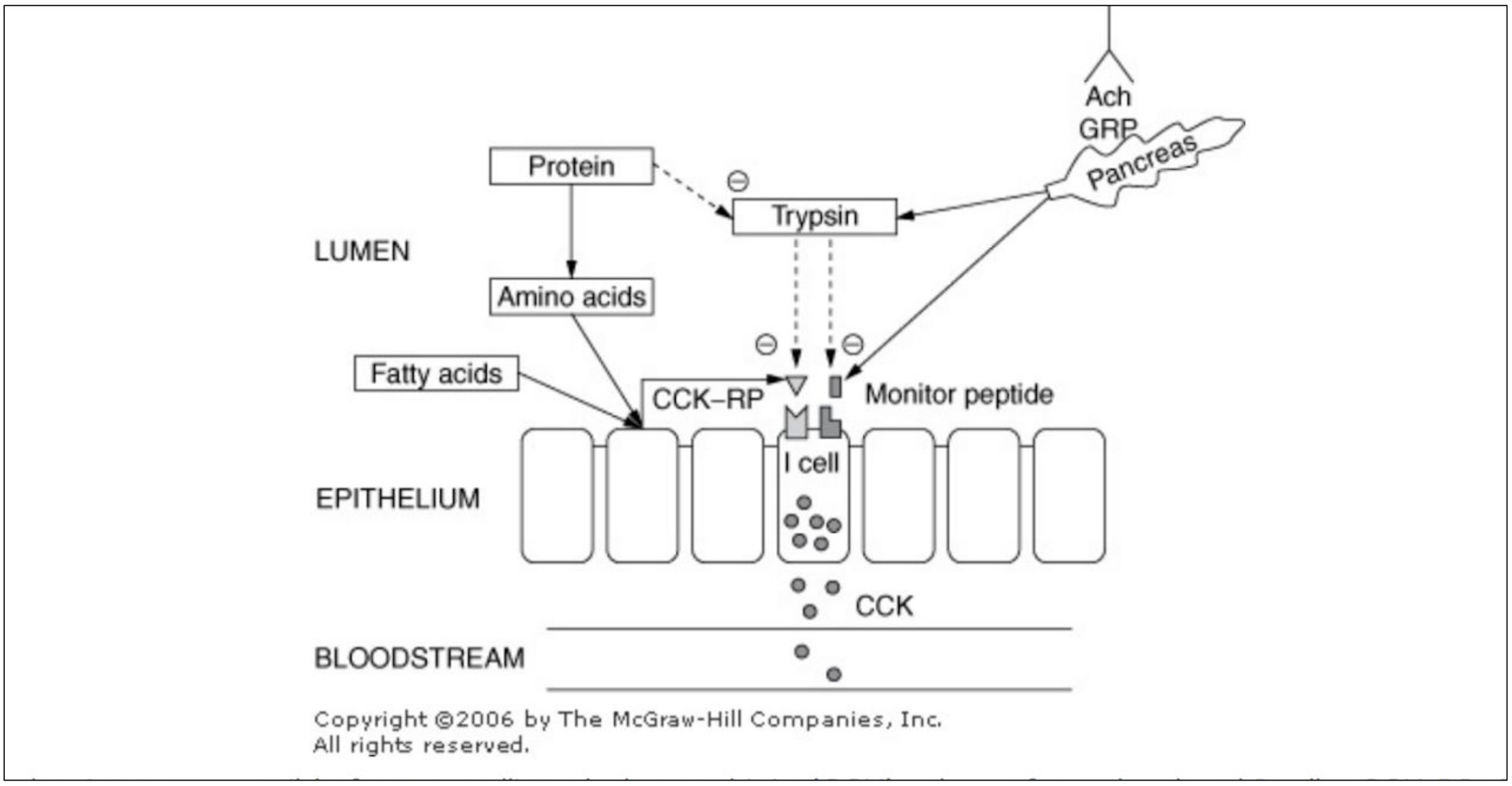

Figure 4-16 Note that trypsin is non-selective in its proteolytic activity, if there is abundance of trypsin in small intestines it will actually breakdown the peptides responsible for CCK secretion (CCK-RP or CCK-releasing peptide plus monitor peptide), thereby maintaining a negative feedback mechanism that protects both the pancreas and small intestines from autodigestion.

Monitor peptide is normally present in small intestines, it is secreted by pancreas as a sensor for chyme content, if there is an abundance of trypsin, this peptide will be degraded by trypsin and it will act less on I cells to secrete CCK. Similarly, CCK-RP is secreted in large amounts in response to chyme contents rich in fats and peptides, when trypsin levels increase CCK-RP will be degraded more and will act less on I cells to secrete CCK. Also, negative feedback.

QUIZ

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1. Pancreatic secretion is stimulated by?
A) Cholecystokinin
B) Secretin
C) Vagal stimulation
D) All of the above factors

2. Which of the following is a function of the pancreas?
A) Increase acidity of chyme
B) Produce enzymes involved in the digestion
C) Secretes mucin to protect duodenal lining
D) Storage of digestive enzymes

3. Chymotrypsinogen is activated by which of the following?
A) Low PH in duodenum
B) Trypsin inhibitor
C) Trypsin
D) Enterokinase

4. Increased HCO_3^- exchange with Cl^- occurs by:
A) Increased secretion of cholecystokinin
B) Decreased secretion of cholecystokinin
C) Increased secretion of secretin
D) Decreased secretion of secretin

5. Pancreatic juice is released in response to:
A) Presence of chyme in stomach
B) Presence of chyme in small intestines
C) Hypoglycemia
D) Hyperglycemia

SHORT ANSWER QUESTIONS

Q1: Why does the pancreas secretes enzymes in an inactive form?

Q2: Compare between phases of pancreatic secretion.

1) Because it secretes digestive enzymes that can digest the pancreas itself, so it secretes the enzymes in an inactive form to be activated in the duodenum.
2)

Phase	Cephalic (20%)	Gastric (5-10%)	Intestinal (70-75%)
Stimulus	Smell, taste, chewing and swallowing	Protein, gastric distention	Amino acid and fatty acids in chyme
Mediator	Vagus nerve	Vagus nerve	hormonal stimulation (Secretin, CCK), enteropancreatic reflexes.

ANSWER KEY: D, B, C, C, B

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REFERENCES

- Guyton and Hall Textbook of Medical Physiology
- Ganong's Review of Medical Physiology