

Physiology of Pancreas

GNT Physiology

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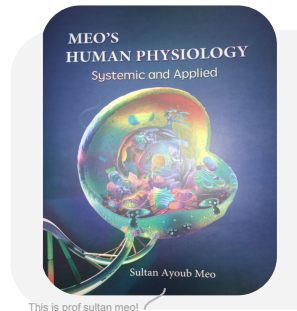
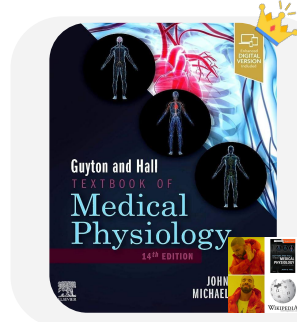
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Objectives

- Functional Anatomy of pancreas
- Major **components** of pancreatic juice **and their physiologic roles**
- Discuss the cellular mechanisms of bicarbonate secretion by the pancreas.
- Cellular mechanisms of enzyme secretion**
- List the proteolytic enzymes synthesized by the pancreas and their target.
- Describe the mechanism of activation of pancreatic enzymes.**
- Discuss the hormonal & neural mechanisms regulating pancreatic secretion.
- Potentialiation of the secretory response
- Release, Stimuli & Actions of Secretin & Cholecystokinin

Resources

Only GI chapters included



This is prof sultan meo!

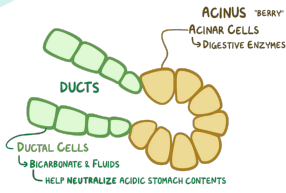
- Click [here](#) for a helpful channel by the team!
- Summary of this Lecture will be in the channel soon..
- For exocrine pancreas.
- For endocrine pancreas.

* وَسَارِعُوا إِلَىٰ مَغْفِرَةٍ مِّن رَّبِّكُمْ وَجَنَّةٍ عَرْضُهَا السَّمَاوَاتُ وَالْأَرْضُ
أَعَدَّتْ لِلْمُتَّقِينَ (133)

وبادروا وسابقوا إلى فعل الخير، والتقرب إلى الله بأنواع الطاعات؛ لتنالوا مغفرة من الله عظيمة،
وتدخلوا الجنة عرضها السماوات والأرض، هيأها الله للمتقين من عباده.
-التفسير الميسر



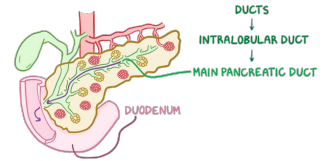
Functional anatomy



Characteristics

- Pancreatic juice is secreted in response to the presence of chyme in the upper portions of the small intestine (duodenum)
- The pancreatic digestive enzymes are secreted by the acini.
- Large volumes of sodium bicarbonate solution are secreted by the small ductules & larger ducts leading from the acini (from duct cells)
- Volume: 1.2-1.5 L/Day / 1 L/Day
- Isotonic → The osmolarity of pancreatic fluid = plasma
- PH: 8 alkaline. Because of bicarbonate solution.

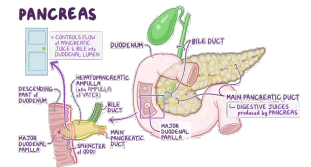
Anatomy



- The Pancreas which lies parallel to and beneath the stomach is a large compound (exocrine & endocrine) gland with most of its internal structure similar to that of the salivary glands.
- The combined product of enzymes & NaCO₃ flows through a long pancreatic duct.
- 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.

Possible SAQ

Function

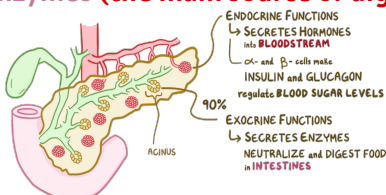


- Pepsin in the duodenum might lead to duodenal ulcer, so we need to neutralize the acidity in the first 3cm of the duodenum.
1. Neutralize the acids in the duodenal chyme to optimum range (pH= 7.0-8.0) for activity of pancreatic enzymes.
 2. To prevent damage to duodenal mucosa by acid & pepsin.
 3. Produce enzymes for the digestion of carbs, fat & protein.

Pancreas divisions

Exocrine

- Constitute 99% of pancreas.
- Made of Acinar gland tissue
- The cells lining the acini are serous cells containing zymogen granules → the precursors of pancreatic enzymes (the main source of digestive enzymes).



Endocrine

- Constitute 1% of pancreas
- Made of Islets of Langerhans.
- Secretes: hormones directly into the blood.
- Secretes 3 hormones:
 1. Insulin from Beta cells (~60% of Islets cells)
 2. Glucagon from Alpha cells (~25%)
 3. Somatostatin from Delta cells (~10%)
- I&2 are crucial for normal regulation of glucose, lipid, and protein metabolism.



Composition & Mechanism



Composition of secretions

Female slides

Organic materials (1 - 2 %)	Inorganic materials (1 %)
<ul style="list-style-type: none"> Mostly enzymes. Secreted from: acinar cells. 	<ul style="list-style-type: none"> Electrolytes. Produced from: the centroacinar & intercalated duct cells. Include: Na^+, K^+, Ca^{++}, HCO_3^-, Cl^-, with greater bulk in the form of NaHCO_3



Mechanism of HCO_3^- formation

[Click here to see the slides' pictures](#)

Important

1

CO_2 and H_2O combine in **ductal** cells to form H_2CO_3 in the presence of carbonic anhydrase.

2

H_2CO_3 dissociates into H^+ and HCO_3^-

3

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

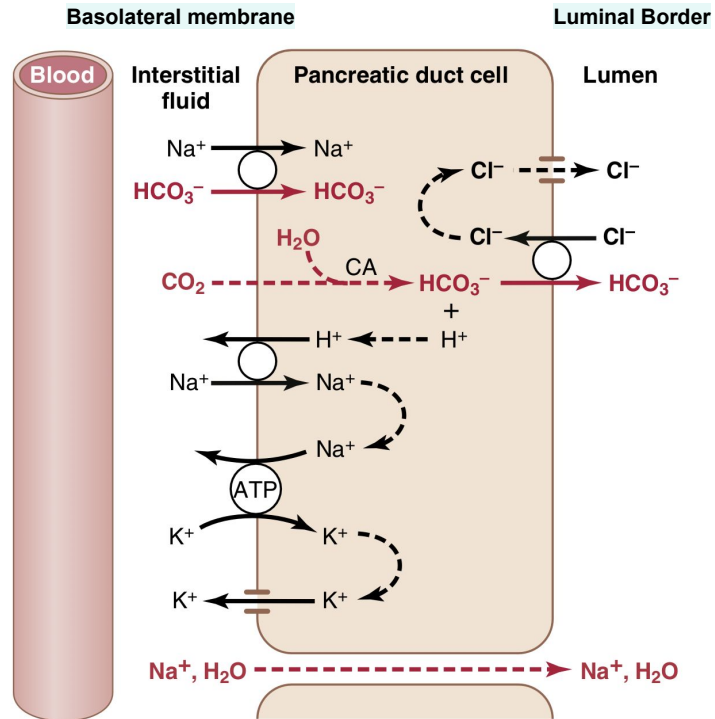
Na^+/H^+ exchanger to work, it needs Na^+ into the cell, this happens by Na^+/K^+ ATPase.

4

HCO_3^- is **secreted** into **pancreatic juice** by $\text{Cl}^-/\text{HCO}_3^-$ exchanger at apical membrane of ductal cells.

Cl^- pumped into the cell

HCO_3^- secreted into the lumen.



Absorption of H^+ causes **acidification** of pancreatic venous blood (**acidic tide**)

In stomach -> Acid secretion -> Alkaline tide.
In pancreas -> Alkaline secretion -> Acidic tide.

" هو هنا **Acidic tide**, بعدها يبمر مع **venous blood from stomach** ويصير **Neutralization** ولذلك **PH** للـ **General circulation** مايتأثر."

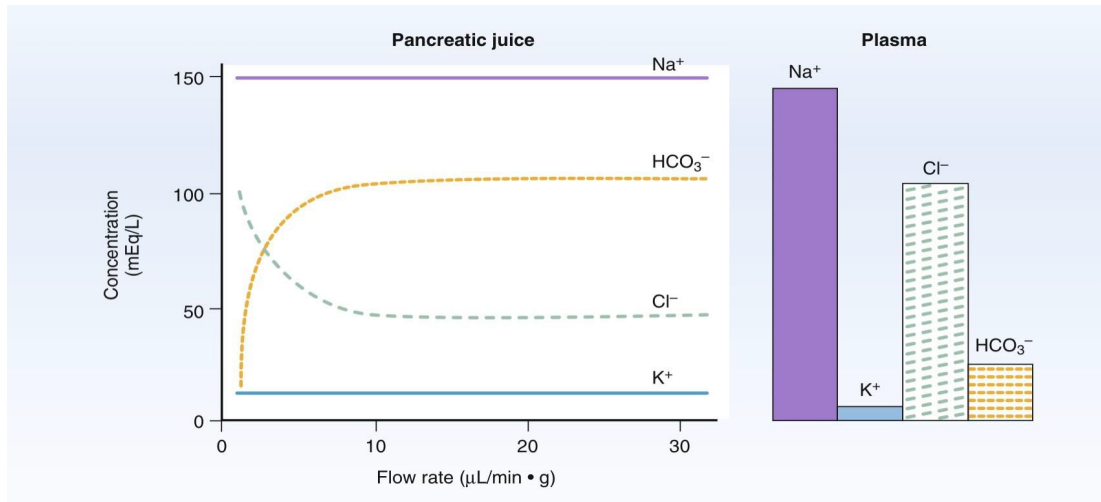


Extra Explanation from the Leader

بيدخل CO_2 داخل الخلية، في وجود CA بيحطه مع المويه اللي موجودة وبيتكون H_2CO_3 ، هذا علطول بيتفكك إلى هيدروجينه و HCO_3^- حلو؟ الهيدروجينه انسوها شوي، بتلاحظون فوق فيه transporter فيبدخل عندنا HCO_3^- إضافية، ليه؟ ما ادري قررت تدخل.. مين دخلها؟
 الـ Na^+ لذلك تعتبر secondary Active transport.
 الآن الـ HCO_3^- بتطلع للـ luminal border بس نحتاج ندخل Cl^- عشان تقدر تطلع، طيب تخيلوا ان كل الكلورايد دخل جوا، يعني خالص الـ Cl^- هل بقدر نطلع HCO_3^- ؟ لا، عشان كذا Cl^- يصير له recycling.
 الهيدروجينه اللي قلت انسوها وين بتروح؟ مهم جداً نعرف انها بتروح لجهة Basolateral border للدم وليس lumen وهذا منطقي لأن احنا نبغى Alkaline solution احنا بالبنتكرياس مو بالـ stomach، حلو؟ وهذا سبب Acidic tide بكل بساطة (ممکن بعضكم يسأل ليه مايصير مثلاً Metabolic Acidosis، السبب هو النوت اللي فوق حقت الدكتور).
 وطبعاً عشان نطلع الهيدروجينه هادي بندخل صوديوم (ونفس فكرة الكلورايد بالضبط، بنحتاج نسوي recycling للصوديوم)
 بالنسبة للمويه بتدخل بالـ Osmosis وهذا سبب ان مافيه فرق مع البلازما، Completely isosmotic bicarbonate solution



Effect of flow Rate on pancreatic secretion



The increase in the pancreatic secretion rate (Secretion velocity):

1. ↑ HCO₃
2. ↓ Cl⁻
3. Na⁺ & K⁺ remain the same in plasma & pancreatic juice

SECRETIONS OF DUCTAL CELLS

SODIUM POTASSIUM
concentrations = PLASMA

CHLORIDE BICARBONATE
DEPEND on PANCREATIC FLOW RATE

VOLUME of SECRETIONS per MINUTE

REGULATED by TRANSPORT CHANNELS

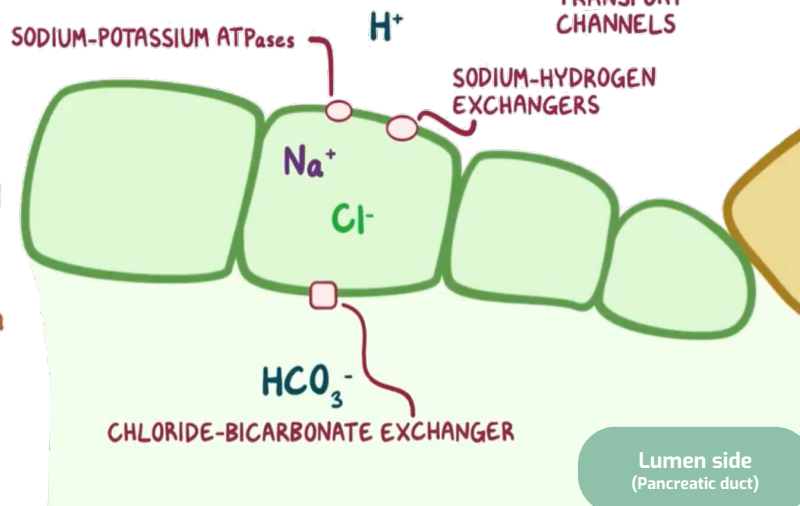
when food is DIGESTED

↑ PANCREAS SECRETION

↑ FLOW RATE

↑ bicarbonate concentration
~ OFFSETS ACIDITY

↓ chloride concentration
~ BEING EXCHANGED



Everything in this pic was mention by the Dr.



pancreatic secretions



Phases of pancreatic secretions

Phase	Cephalic Phase 20% of pancreatic secretion Will be affected in case of vagotomy	Gastric Phase 5-10% of pancreatic secretion Will be affected in case of vagotomy	Intestinal Phase 70-75% of pancreatic secretion
Stimulus	<ul style="list-style-type: none"> • <u>Smell, Hearing*</u> • Swallowing • Taste • Chewing 	<ul style="list-style-type: none"> • Gastric distention • Presence of proteins 	<ul style="list-style-type: none"> • Fatty acids • Acidity of the chyme (H⁺)
Mediator	Ach by the vagal nerve	<ul style="list-style-type: none"> • Vago-vagal reflex • Ach by the vagal nerve 	<ul style="list-style-type: none"> • Secretin • CCK • Vago-vagal reflex

* Due to presence of food in the mouth or even in absence of food in the mouth, eg, Hearing sounds of food preparation! And this is called conditional reflex.

What's the conditional Reflex?



كنت بشرحها بس مافي أحسن من دكتور ناجي :
الدقيقة: 45:50



Secretions

- Pancreatic secretions contain many enzymes for digesting proteins, carbohydrates, fats & large quantities of HCO₃ ions.

Proteins

Endopeptidases:

- Trypsin
- Chymotrypsin

Exopeptidases:

- Carboxypeptidase

Fat

- Pancreatic lipase
- Cholesterol esterase (Carboxyl Ester hydrolase)
- Phospholipase

DNA & RNA

Nucleases

- Ribonuclease
- Deoxyribonuclease

Carb

- Pancreatic amylase

[Click for a summary from the female slides](#)
"Please don't skip"

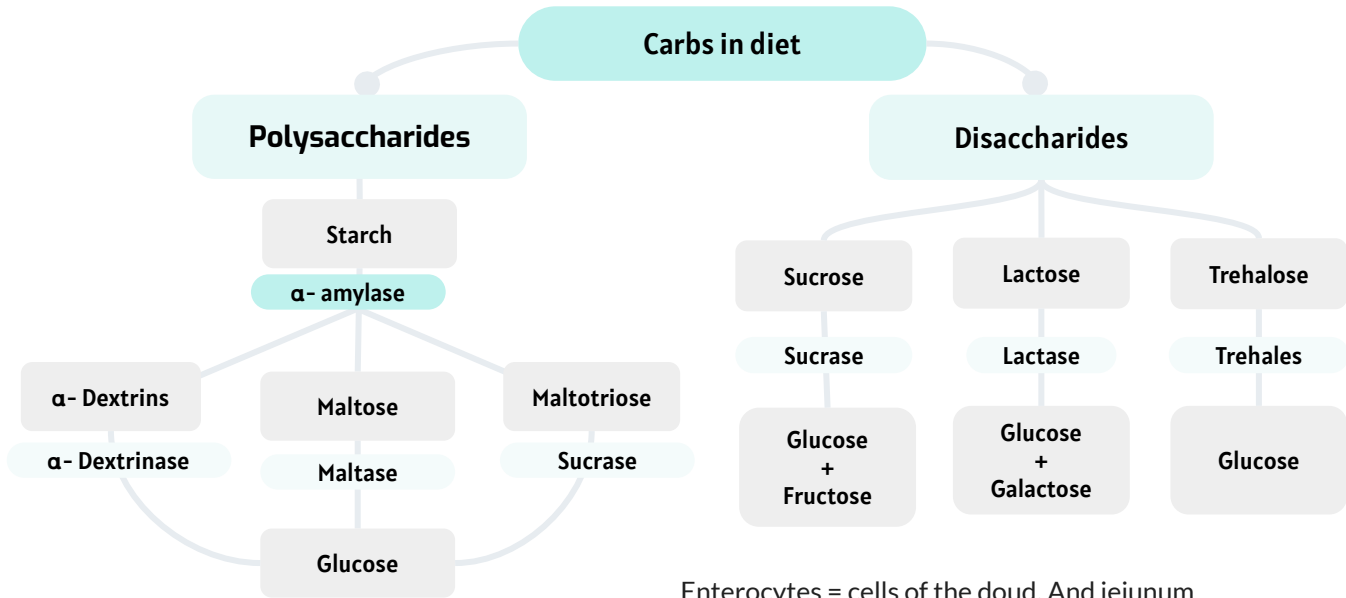


The Role of Pancreas in Digestion



Carbohydrates

- The pancreatic enzyme for digesting **carbohydrates** is **pancreatic amylase**, which hydrolyzes starches, glycogen and most other carbohydrates (**except cellulose**) to form mostly disaccharides (**maltose**) and a few tri-saccharides.



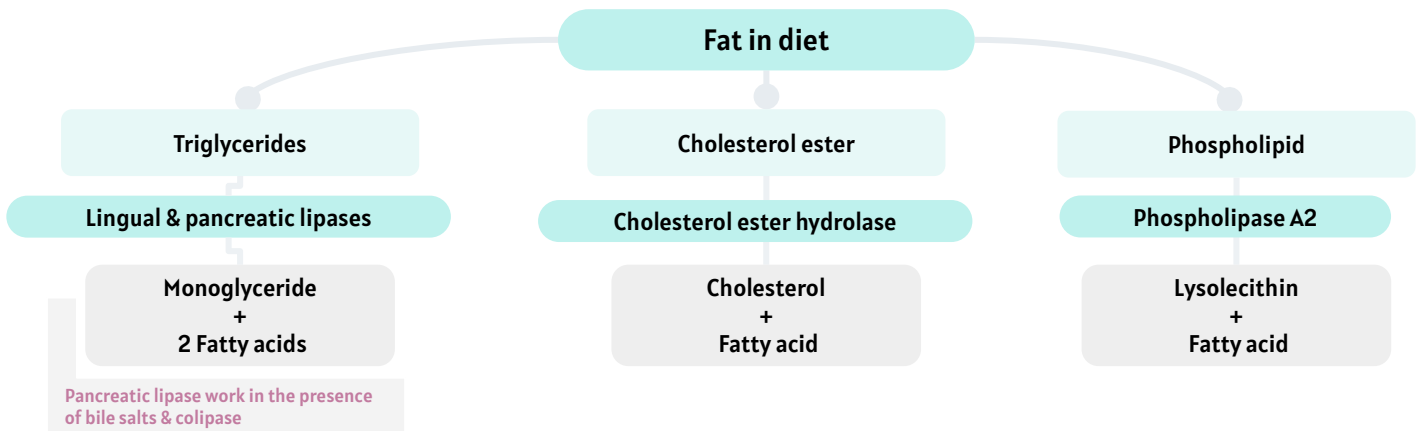
Enterocytes = cells of the duod. And jejunum
Brush border secretes these enzymes in the duodenum and jejunum



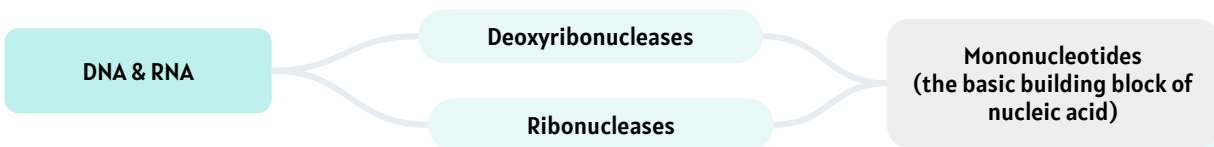
Fats

- The main enzymes for **fat** digestion are:
Pancreatic lipase, Cholesterol esterase & Phospholipase.

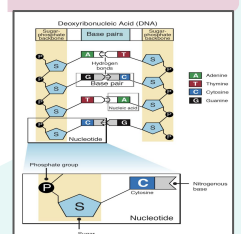
- Pancreatic lipase: is the most important fat splitting enzyme. It breaks TG into MG and 2 FAs in the presence of bile salts and colipase.
- Cholesterol esterase: which liberates cholesterol and FA.
- Phospholipase A2 :which splits phospholipids into lysolecithin & FA.



Nucleic Acid



Female slides





The Role of Pancreas in Digestion Cont.



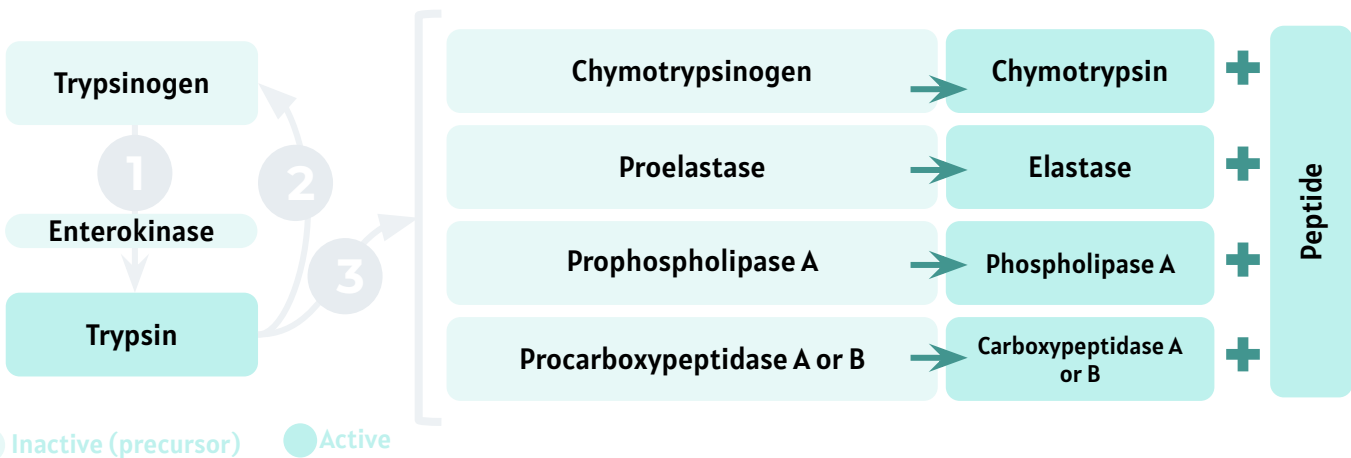
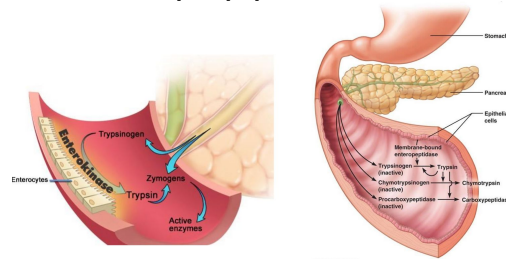
Protein

The suffix -ogen or prefix pro- indicates the enzyme is secreted in an inactive form

Important

- The most important pancreatic enzymes for digesting proteins are: **Trypsin**, **Chymotrypsin** and **Carboxypolypeptidase**.

	Trypsin	Chymotrypsin	Carboxypolypeptidase
Synthesis	<ul style="list-style-type: none"> When first synthesized in the pancreatic cells, the proteolytic digestive enzymes are in the <u>inactive forms</u>: Trypsinogen, Chymotrypsinogen and Procarboxypolypeptidas. They become activated only after they are secreted into the intestinal tract. 		
Activation	<ul style="list-style-type: none"> Trypsinogen is activated by Enteropeptidase (enterokinase), an enzyme secreted by the intestinal mucosa when chyme comes in contact with the mucosa. Trypsinogen can be activated autocatalytically by trypsin formed from previously secreted trypsinogen. The most important pancreatic enzyme to be activated. 	<ul style="list-style-type: none"> Chymotrypsinogen and Procarboxypeptidase are activated by trypsin to form chymotrypsin and carboxypolypeptidase. 	
Function	<ul style="list-style-type: none"> Trypsin & Chymotrypsin (Endopeptidases) → Split whole and partially digested proteins into peptides of various sizes. Do <u>not</u> cause release (break down) of <u>individual amino acids</u>. 		<ul style="list-style-type: none"> Carboxypeptidase (Exopeptidases) → Splits some peptides into individual amino acids at the carboxyl terminus → completing the digestion of some proteins to amino acids



Important

1- Enterokinase is an enzyme that is secreted by brush border of small intestine and activate trypsinogen.

2- **Trypsin autocatalytically activates itself to active other trypsinogen, and other enzyme.**

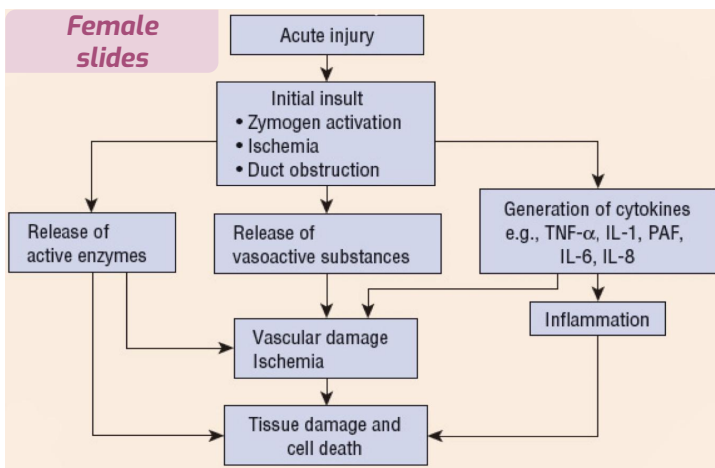
**If it gets inhibited (trypsin) all of these enzymes will stop working (inactive)



Trypsin Inhibitor

Secretion of Trypsin Inhibitor Prevents Digestion of the Pancreas Itself. *How?*

- 1 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.
- 2 The **same cells that secrete proteolytic enzymes into the acini of the pancreas secrete another substance called trypsin inhibitor**, which is formed in the cytoplasm of the glandular cells
- 3 It **prevents** activation of trypsin both inside the secretory cells and in the acini and ducts of the pancreas.
- 4 Because trypsin activates the other pancreatic proteolytic enzymes, therefore trypsin inhibitor prevents activation of the other enzymes as well.
- 5 When a duct is blocked, trypsin inhibitor can not inhibit activation of accumulated enzymes which will be activated and digest the pancreas in few hours.



Clinical application: acute pancreatitis

Accumulation of the enzymes in the pancreas due to obstruction or other cause (e.g. Zollinger-ellison), will lead autoactivation of pancreatic enzymes inside the pancreas, leading to acute pancreatitis



Multiplicative / Potentiation Effect

Important

When all different stimuli of pancreatic secretion (acetylcholine, cholecystokinin, and secretin) occur at once, then the total secretion is far **greater than the sum of the secretions caused by each stimulus separately**.

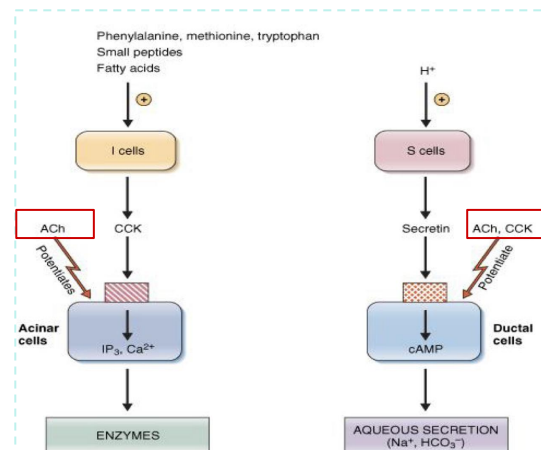
The stimuli are said to "**multiply**" or "**potentiate**" one another.

Usually, pancreatic secretions are the result of multiple stimuli rather than one stimulus.

Example:

- Ach alone: 2
- CCK alone: 3
- Secretin alone: 2
- Total secretion is Not the sum (7)! These stimuli are said to multiply/ potentate eg(12)

(numbers are random, just to get the idea)





Regulation of Pancreatic Secretion

I. Vagus nerve

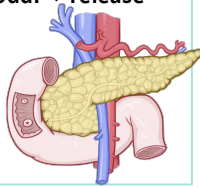
-Act on acinar cells.

-Functions:

Acetylcholine from parasympathetic vagus nerve endings and from other cholinergic nerves in the enteric nervous system →

1) increase in enzyme secretion-fluid & HCO_3^- .

2) Vagus nerve stimulation relaxes (opens) the sphincter of Oddi → release pancreatic enzymes.



2. Cholecystikin (CCK)

-Act on activating acinar cells

-Secreted by: I cells in the duodenal (enteroendocrine cells) & jejunal mucosa.

-Stimulated by: food entering the small intestine containing:

- 1) Fat (long-chain fatty acids).
- 2) Proteoses & peptides (Partial protein degradation products).

-Function: ↑Pancreatic digestive enzymes

CCK: relaxes sphincter of Oddi. Most powerful hormone acting on sphincters.

3. Secretin

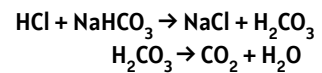
-Act on activating ductal cells

-Secreted by: S cells in duodenal & upper jejunal mucosa (present as presecretin).

Stimulated by: increased chyme acidity in the duodenum and jejunum luminal pH < 4.5

-Function: stimulate secretion of large quantities of H_2O and NaHCO_3 solution from ductal cells → **neutralize chyme acidity.**

The secreted HCO_3^- concentration = 145 mmol/L ~5X normal but a low concentration of Cl^- .




- Ach & CCK stimulate the acinar cells of the pancreas, causing production of large quantities of pancreatic digestive enzymes but relatively small quantities of H_2O & electrolytes to go with the enzymes.

- Secretin (in contrast) stimulates secretion of large quantities of H_2O and NaHCO_3 solution by the pancreatic ductal epithelium.

-Secretin:
When acid chyme with PH less than 4.5-5 enters the duodenum from the stomach, it causes duodenal mucosal release and activation of secretin, which is then absorbed into the blood.

Trypsin inhibitors (TI) get degraded in the duodenum to let the trypsin function.

After secretin secretion, it is then absorbed into the blood. Cholecystikin, like secretin, passes by way of the blood to the pancreas

	Cholecystikin (CCK)	Secretin Important
Information	This 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.	Secretin is present in an inactive form:prosecretin
Function	<ul style="list-style-type: none"> ● Augments stimulation of HCO_3^- & H_2O secretion by secretin. ● Stimulates pancreatic enzyme secretion. ● Stimulates intestinal motility & relaxes ileocecal sphincter. ● Inhibits stomach contraction moderately & slows its emptying. ● Contracts gallbladder, relaxes sphincter of Oddi and causes bile discharge into intestine. ● Has trophic effect on pancreas. ● Maybe concerned with the mechanism of satiety. 	<ul style="list-style-type: none"> ● Augments stimulation of enzyme secretion by CCK. ● Stimulates pancreatic secretion rich in HCO_3^- & H_2O from duct cells. ● Stimulates hepatic bile flow & HCO_3^- secretion ● Inhibits gastric acid secretion & gastrin release, but it stimulates pepsin secretion. ● Inhibits gastric motility, contracts pylorus & slows gastric emptying, relaxes LES. ● Inhibits intestinal motility & contracts ileocecal sphincter.

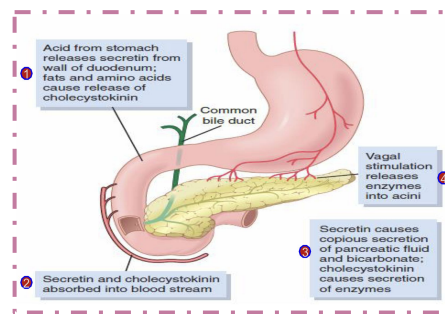
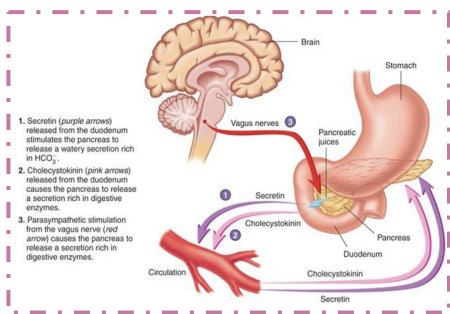


Cell types of the pancreas:

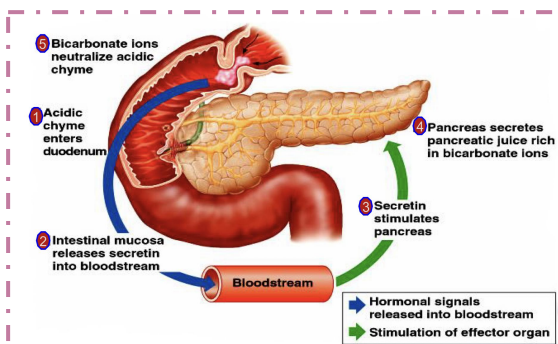
Ductal cells	Acinar cells
Secretes a HCO_3^- rich fluid that alkalinizes & hydrates (H_2O) the protein-rich secretion of acinar cells [HCO_3^-] = 145 mEq/L	Secrete a protein-rich (digestive enzymes) secretion in an isotonic plasma-like fluid (so enzymes will be thick in absence of ductal cells effect).
Because there is high amount of enzymes secreted from acinar cells in a little solution, it's thick → needs solution to facilitate its move until they arrive to the duodenum to prevent duct blockage → this solution is provided by ductal cells	
<ul style="list-style-type: none"> Constitute 75% of pancreatic secretion. Stimulated by Secretin secreted by S cells. 	<ul style="list-style-type: none"> Constitute 25% of total pancreatic secretion. Stimulated by CCK secreted from I cells & Ach.
<ul style="list-style-type: none"> Effects of Secretin are potentiated by CCK & Ach. 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. The stimuli are said to "multiply" or "potentiate" one another. 	<p>Why don't these enzymes digest the pancreas?</p> <ul style="list-style-type: none"> Secreted as proenzymes (inactive form) which get activated in the lumen of the intestine. If they one of enzyme activated in the pancreas for any reason trypsin inhibitor will do its role of protection. The same cells secrete a substance "trypsin inhibitor".

Pictures from the slides

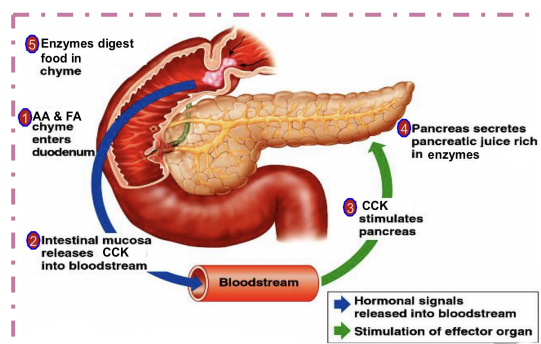
Neural and Hormonal Control of Pancreatic Secretion



Regulation by Secretin



Regulation by CCK





Doctors' Notes

1: The Main pancreatic duct joins the duct from the liver (common bile duct) and both of them open in 2nd portion of duodenum through "papilla of Vater" surrounded by Oddi sphincter.

2: Sphincter of Oddi is regulated by CCK:

- Relax it -> secretions go into duodenum.
- Also squeeze the bile duct and pancreatic duct -> release components into duodenal lumen.

3: Major functions of pancreatic secretions:

1- Neutralise acid in "duodenal" chyme,

- Possible SAQ, what's the importance of that?

1- To prevent damage to duodenal mucosa.

2- To provide optimal PH for action of intestinal enzymes.

- What's the main source of digestive enzymes of GIT? Pancreas! Because it produces enzymes for all types of food stuff (proteins, carb, etc..)

4: All gastrointestinal secretions are: Isosmotic Except (**saliva, Hyposmotic**)

salivary = Hyposmotic الدكتور والدكتور كلهم قالوا معلومة الـ

5: Enteropeptidase is brush border enzyme and it's NOT in pancreatic tissue/duct!

- Only trypsinogen is (Auto-catalytically) activated.
- Key reaction in activation of pancreatic proteolytic enzymes is the: Release of **trypsin**

6: Pancreatic Amylase: hydrolyse carbs to —> **MALTOSE** (disaccharide)

"Pancreatic amylase vs salivary amylase

Which one of them is more powerful?

Both have same potency but in the mouth food stays for short duration (not sufficient for the activity of the enzyme), So **pancreatic amylase has physiological importance** because food (chyme) stays for sufficient time for the action of pancreatic amylase "

"Gastric Lipase - pancreatic lipase - intestinal lipase, Which is more sufficient?

Pancreatic Lipase, -> لأنه اذا قل -> loss of fat in stool"

- More activation of pancreatic acinar cells -> more production of isotonic solution in ductal cells .

هاذي نوت الدكتور، وموجوده بشكل مشابه بسلايدات الدكتور:

"Hco3 conc. increases with increasing secretion rate"

7: Secretin and CCK:

الدكتور: site of release /stimulus/ action تتنحفظ.

الدكتور: "هذا من الجدول حقي اللي هو جزء من حياتي وحيكون جزء من حياتك غصباً عنك"
أي جدول؟ هنا

8: Functions of Secretin:

الدكتور: "هذا مهم اوي اوي يعني تعرفوه كويس جداً"

9: Functions of CCK:

This function is so important: Contracts Gall bladder, Relaxes sphincter of Oddi.

TEST YOURSELF !

MCQ:

Q1) Pancreatic secretion is stimulated by?

- A) CCK B) Secretin C) Vagal stimulation D) all of them

Q2) Trypsinogen is activated by?

- A) Enteropeptidase B) Exopeptidases C) autocatalytically D) A+C

Q3) Which of the following is a function of the pancreas?

- A) increase acidity of chyme B) produce enzymes involved in digestion C) secretes mucin to protect duodenal lining D) storage of digestive enzymes

Q4) What's the type of secretion pancreatic acini produces?

- A) isotonic B) hypotonic C) hypertonic D) acidic

Answers: Q1:D | Q2:D | Q3:B | Q4:A

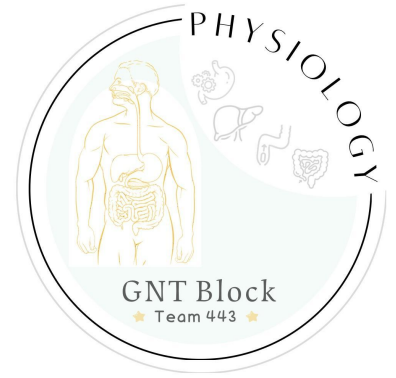
SAQ:

Q1) Give two examples of enzymes for each of the following classification of pancreatic enzymes:

- A) **proteolytic enzymes:**
1. endopeptidases
2. carboxypeptidases A and B
- B) **Amylolytic enzymes :**
1. Alpha-Amylase
2. Lipases
- C) **Nuceolytic enzymes:**
1. Ribonuclease
2. Deoxyribonuclease

Q2) Compare between phases of pancreatic secretions?

Phase	Cephalic	Gastric	Intestinal
Stimulus	Smell, taste, chewing, swallowing	Protein, Gastric distention	Fatty acid, acidity in chyme
Mediator	Neural (Vagus nerve)	Neural (Vagus nerve "Vago-vagal reflex")	Hormonal stimulus (CCK, Secretin), Neural(vagus nerve "vago-vagal reflex").



The BEST

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