Exocrine Pancreas Physiology

Pancreatic Anatomy

Pancreatic secretion

Pancreatic enzymes

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NASPGHAN
Physiology Education Series

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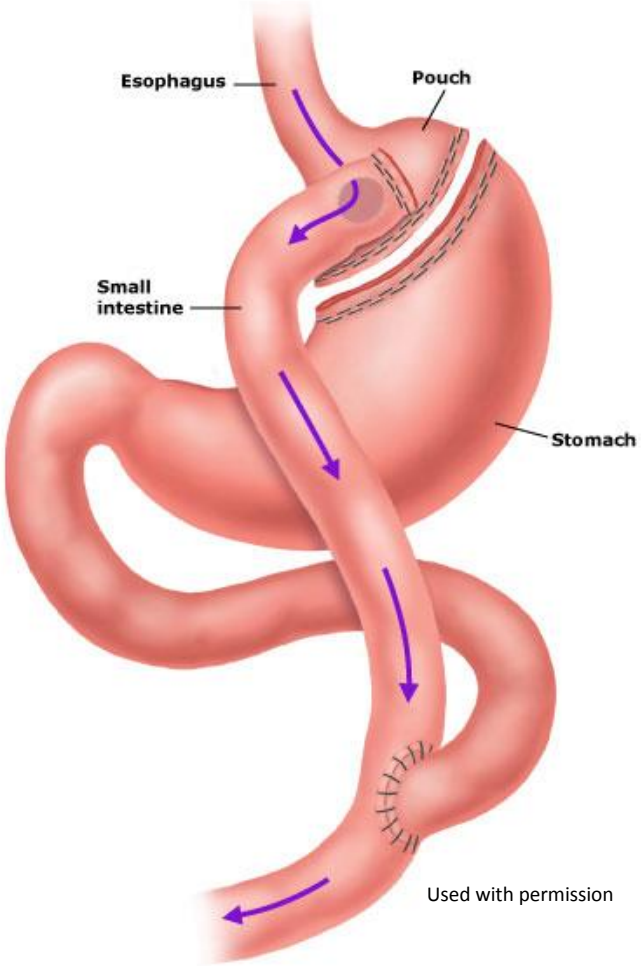
Learning Objectives

- Understand the normal development and anatomy of the pancreas
- Understand the stimuli and cellular factors giving rise to pancreatic secretion
- Know the mechanisms by which pancreatic enzymes are activated and remain functional
- Be aware of age-related deficiency in exocrine pancreatic function

Night blindness

- A young man with morbid obesity undergoes roux-en-y gastric bypass.
- 1 year later he notices that in the evening he falls down his stairs.
- Vitamin A deficiency is diagnosed.



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Understanding the physiology of pancreatic and bile secretion, intraluminal lipolysis, and micellar function explains why this happens!

http://www.citelighter.com/science/surgery/knowledgecards/gastric-bypass

Pancreas Physiology Overview

- Bulk of bicarbonate secretion (more than what secreted in bile and from duodenum)
- Enzymes for intra-luminal digestion
- Secretin and CCK regulate
- Maturational pancreatic insufficiency

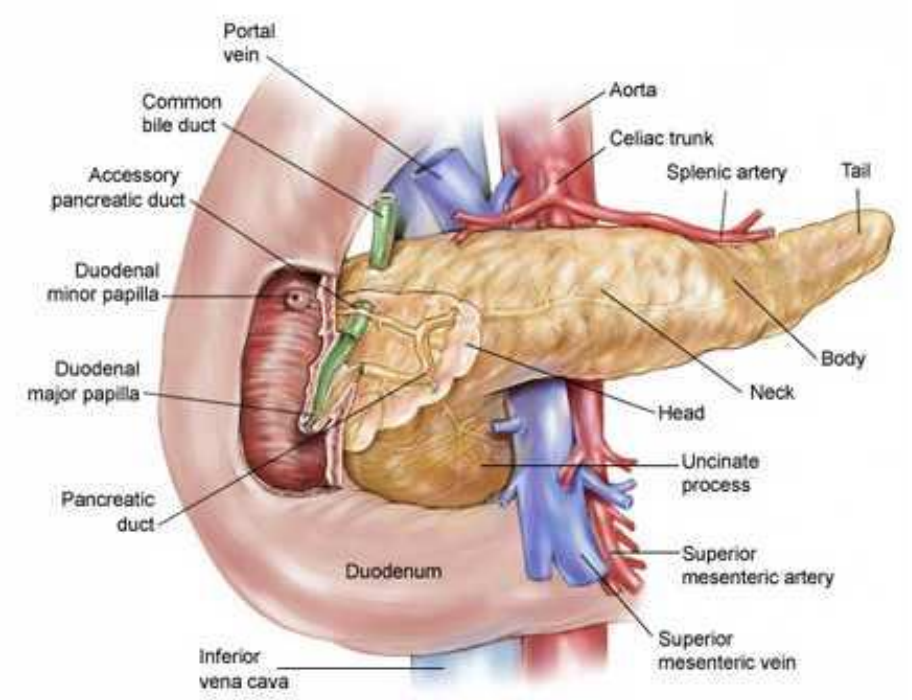

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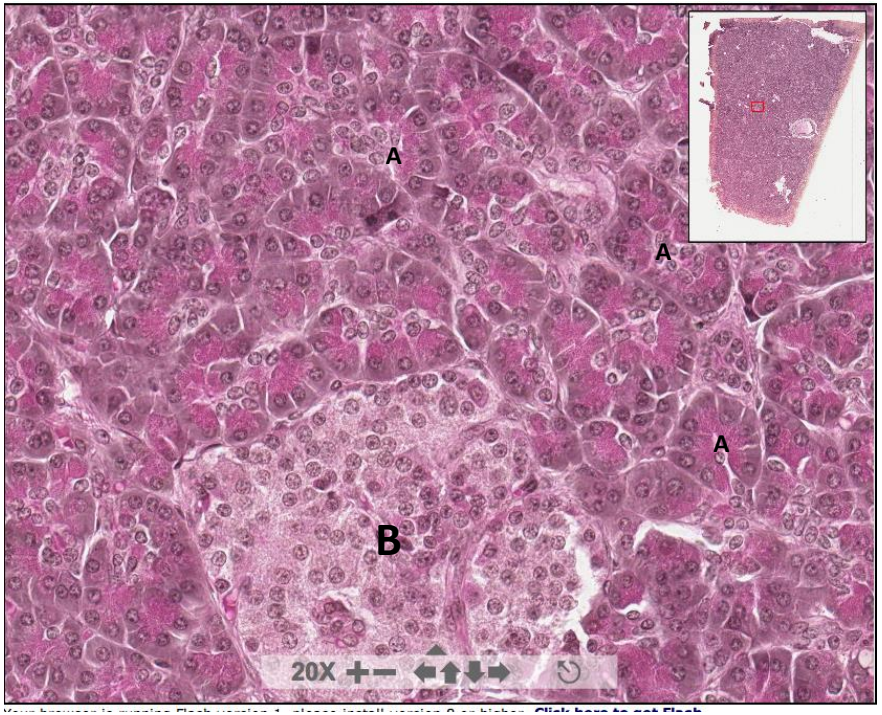
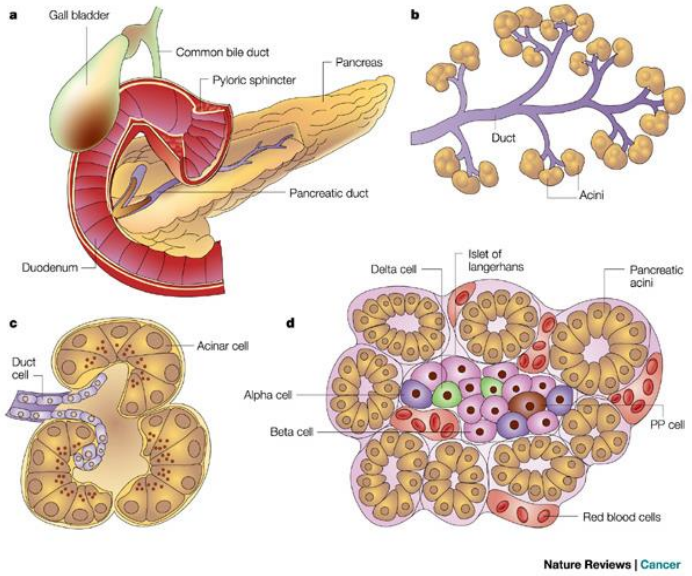
Image from http://www.aboutcancer.com/pancreas1.htm

Pancreatic Development

- See *Embryology and Anatomy of the Gastrointestinal Tract*

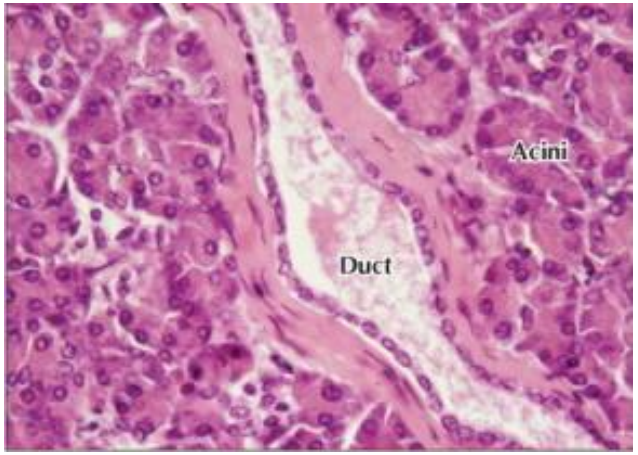
Pancreatic Microanatomy





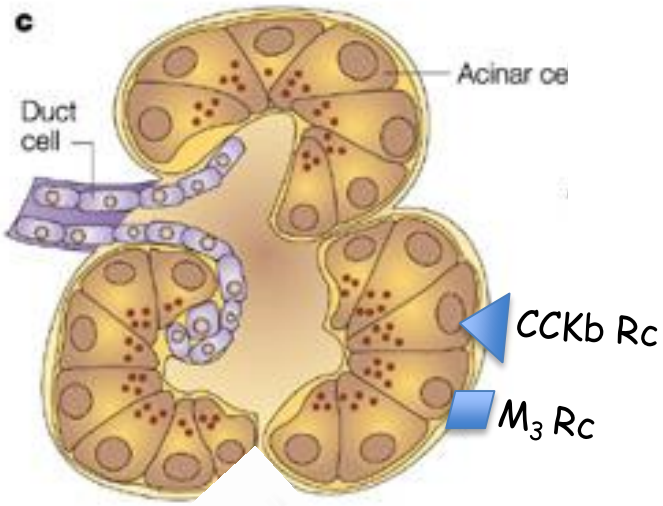
A. Exocrine pancreas-- ascinar cells filled with secretory granules, cuboidal duct cells secrete bicarbonate-rich fluid

B. Endocrine pancreas– Islet of Langerhans



Nature Reviews Cancer **2**, 897-909 (December 2002) used with permission

Pancreatic acinar cell function



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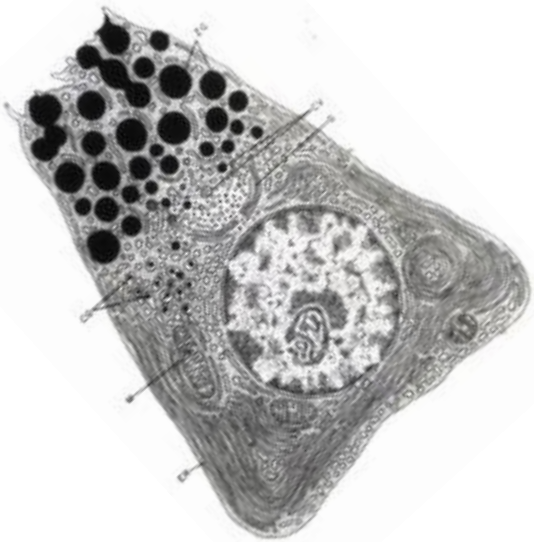

Acinar cell

- Pancreatic enzymes packaged awaiting signal
- Stored and released in dormant conformation
- Effectors for release are neural and endocrine factors
  - **CCK released from I cells in duodenum**
  - Vagal effectors at M_3 receptors
  - Other ENS effectors --ascinus cells have Rcs for VIP, GRP

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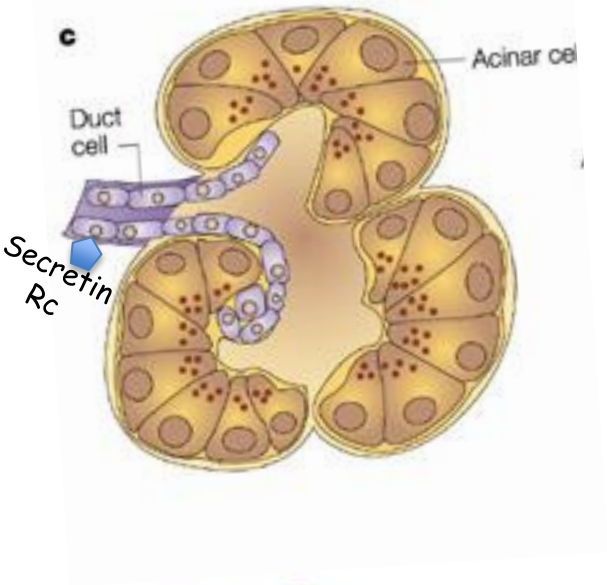
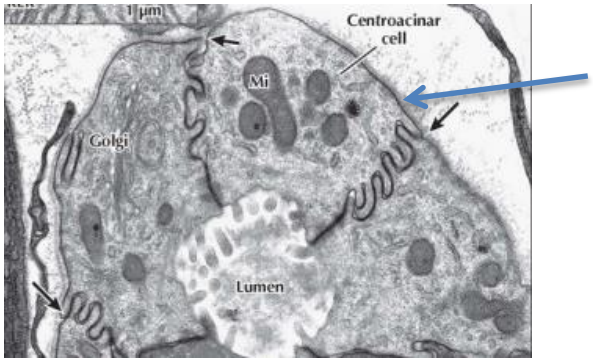
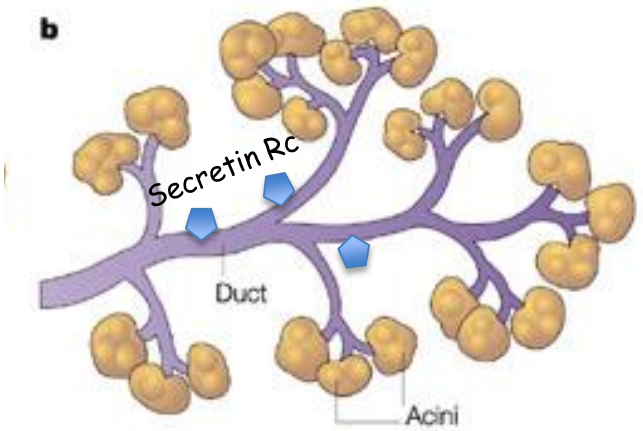
Pancreatic duct cell function

- Washes enzymes into and through the ducts into duodenum
- Prodigious amount of Na+ bicarbonate and water produced
- Neutralizes acidic chyme for optimal enzyme function
- Key effector is **Secretin made in duodenal S cells**
- Subsidiary roles for vagus and CCK
- Adult 1.5-2.5L of fluid/day





Duct cell



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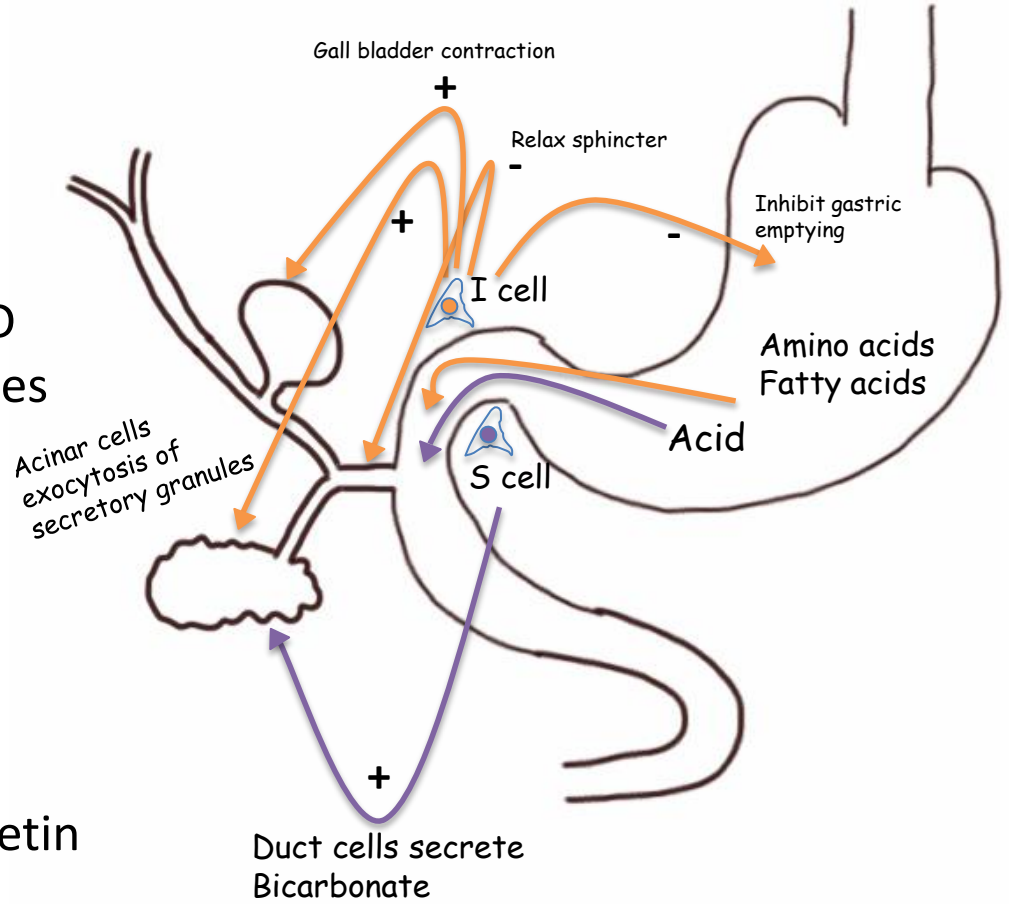
Nature Reviews Cancer **2**, 897-909 (December 2002)
Ovalle & Nahirney: Netter's Essential Histology, 1st ed.

Acinus and Duct physiology

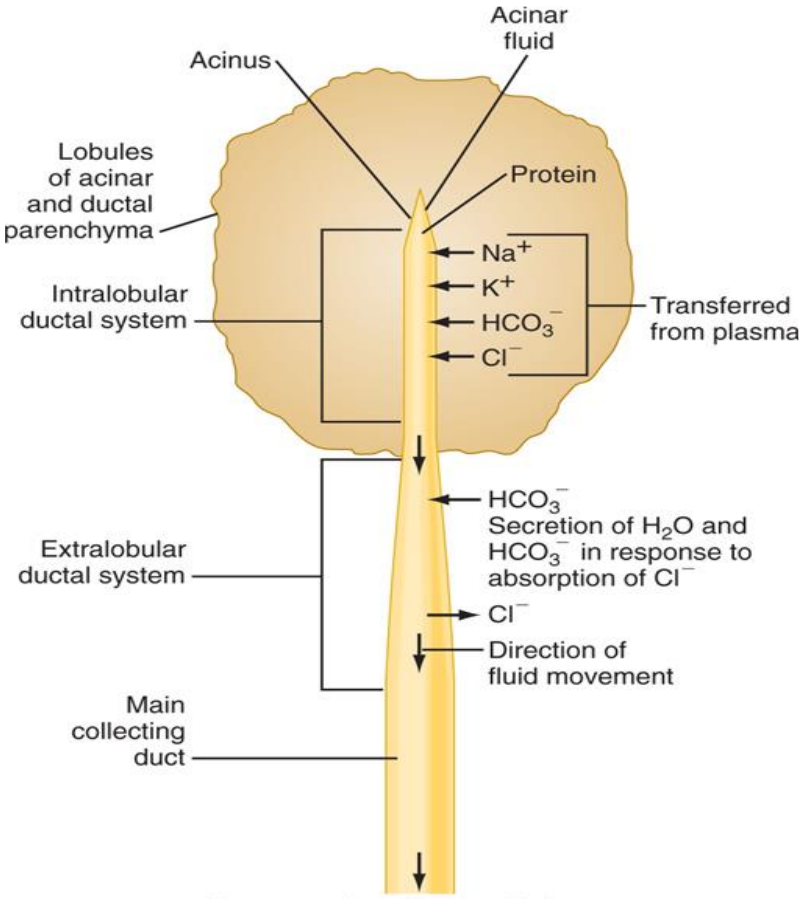
Organ system-based Regulation

- S cells Secretin- '**pH sensor**'
  - pH <4.5➔ activation
- I cells CCK- '**food sensor**'
  - Fatty and amino acids
  - Endocrine mechanism AND Vago-vagal reflex (CCK activates afferent vagus)
- CCK influences the following
  - GB contract
  - Sphincer of Oddi relax
  - Stomach ↓emptying
  - Ascini release enzymes
- Synergy between CCK and Secretin

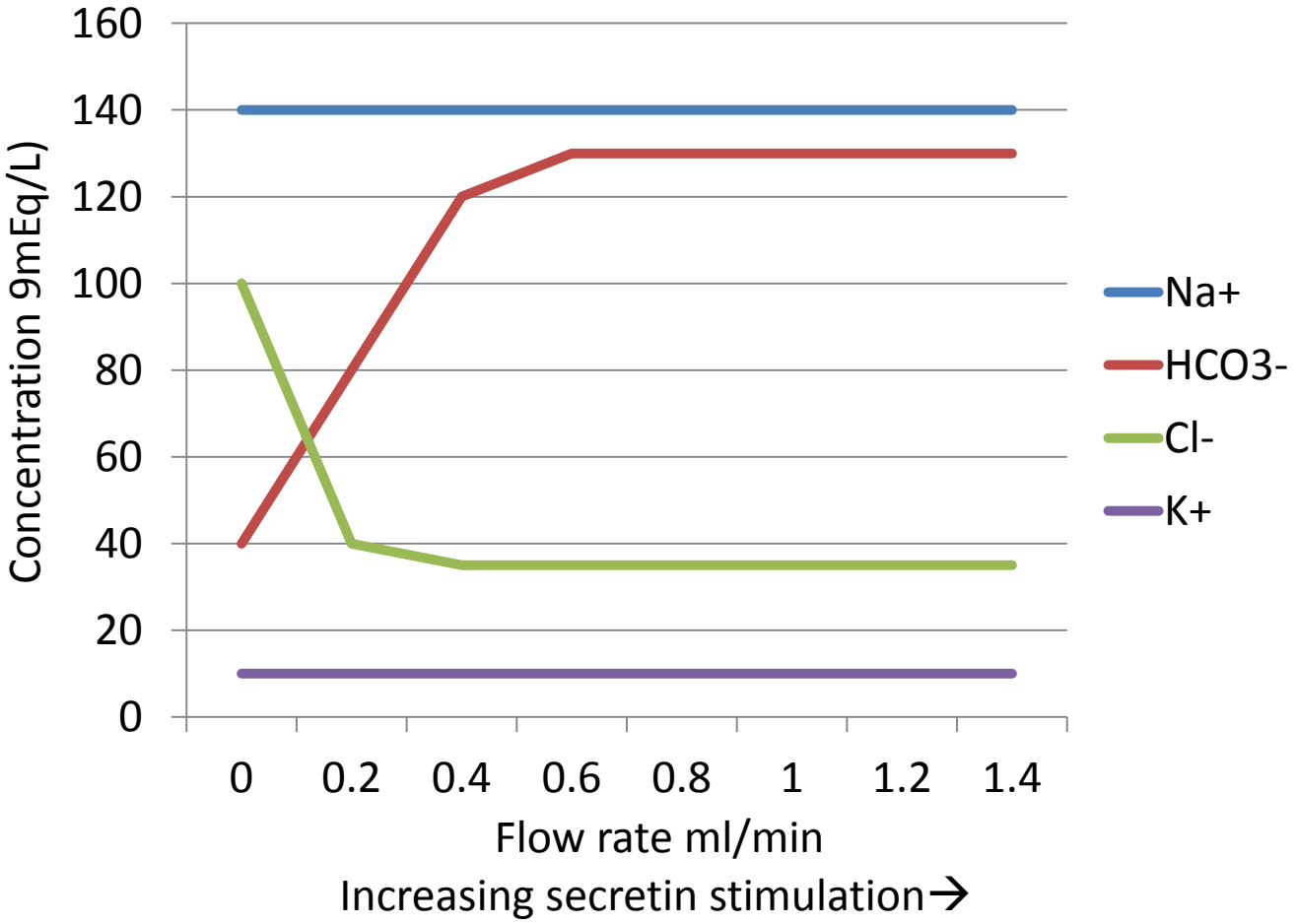


Generation of Pancreatic Juice

- Adults make ~2L/day (resting 0.2ml/min, stimulated 4ml/min)
- Acinar electrolyte [ ]= plasma
- Duct modifies secretion by exchanging bicarbonate for chloride
- Paracellular water/Na+ secretion
- Pancreatic juice Osmolality = plasma

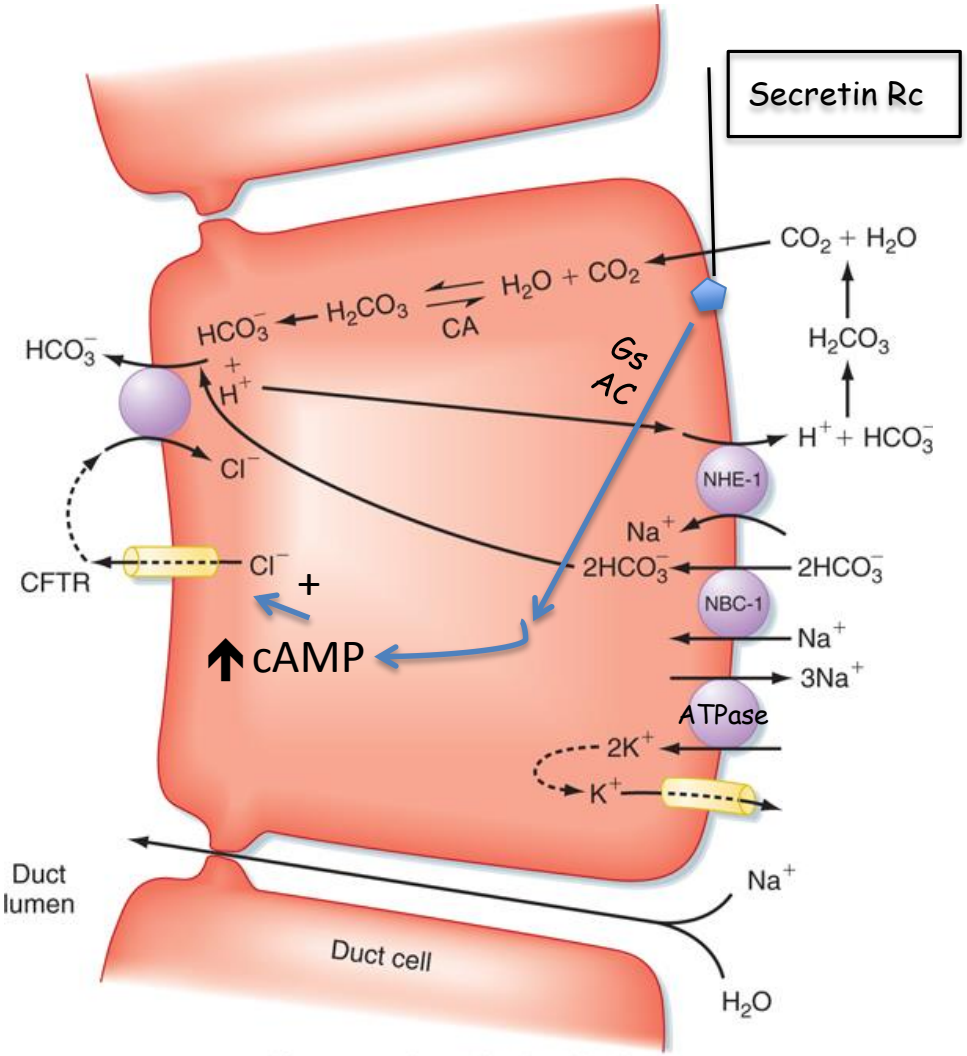


Under influence of secretin, pancreatic juice rich in bicarbonate, low in chloride



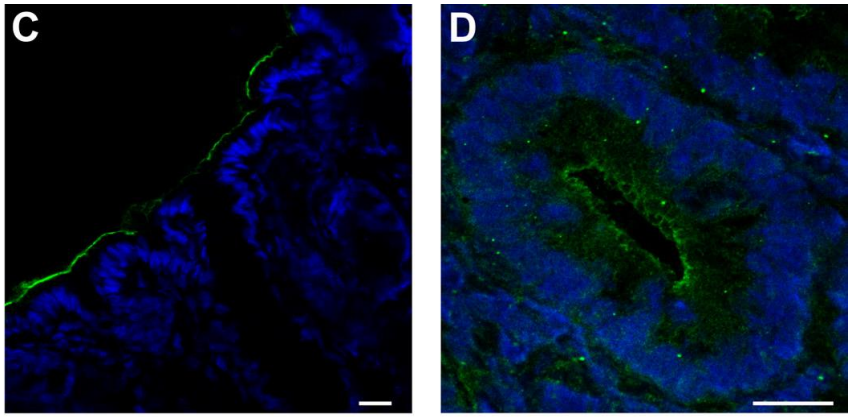
Pancreatic Juice Production- Cellular Model

- CFTR on apical membrane; channel opening drives bicarb and fluid secretion (NB: **CFTR can conduct bicarbonate as well**)
- Chloride recycled while bicarbonate accumulates in luminal fluid
- Bicarbonate derived from gastric 'alkaline tide' and cytoplasmic CA



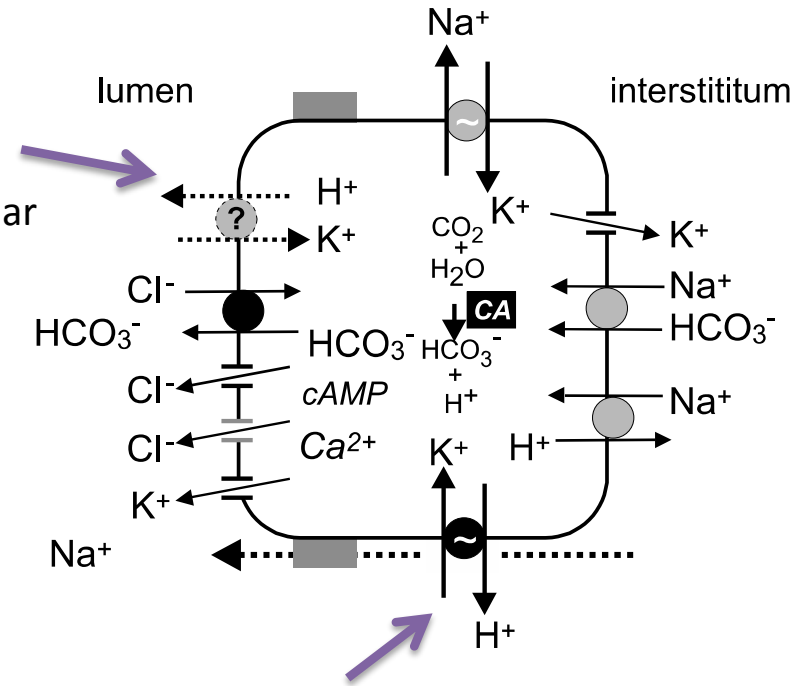
CA carbonic anhydrase

Something New- Proton Pumps on Pancreatic Duct cells?



Rat pancreas, secretin stimulated; red label gastric HK ATPase; green label non-gastric HK ATPase, blue label nuclear stain

Question is how duct cell achieves such a high concentration of bicarbonate in the lumen without acidifying the cytosol?

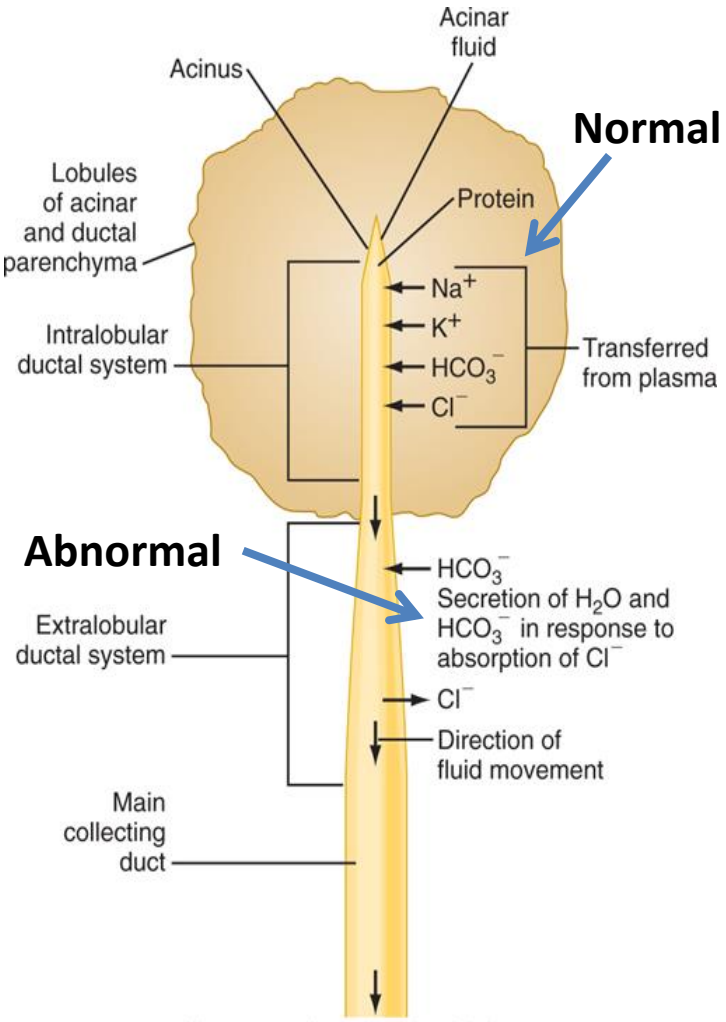


Implications for understanding cystic fibrosis and impact of PPIs on normal pancreatic function.

THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL.286,NO.1,pp.280–289, January7,2011

Clinical Correlation- ductular cellular dysfunction- Cystic Fibrosis

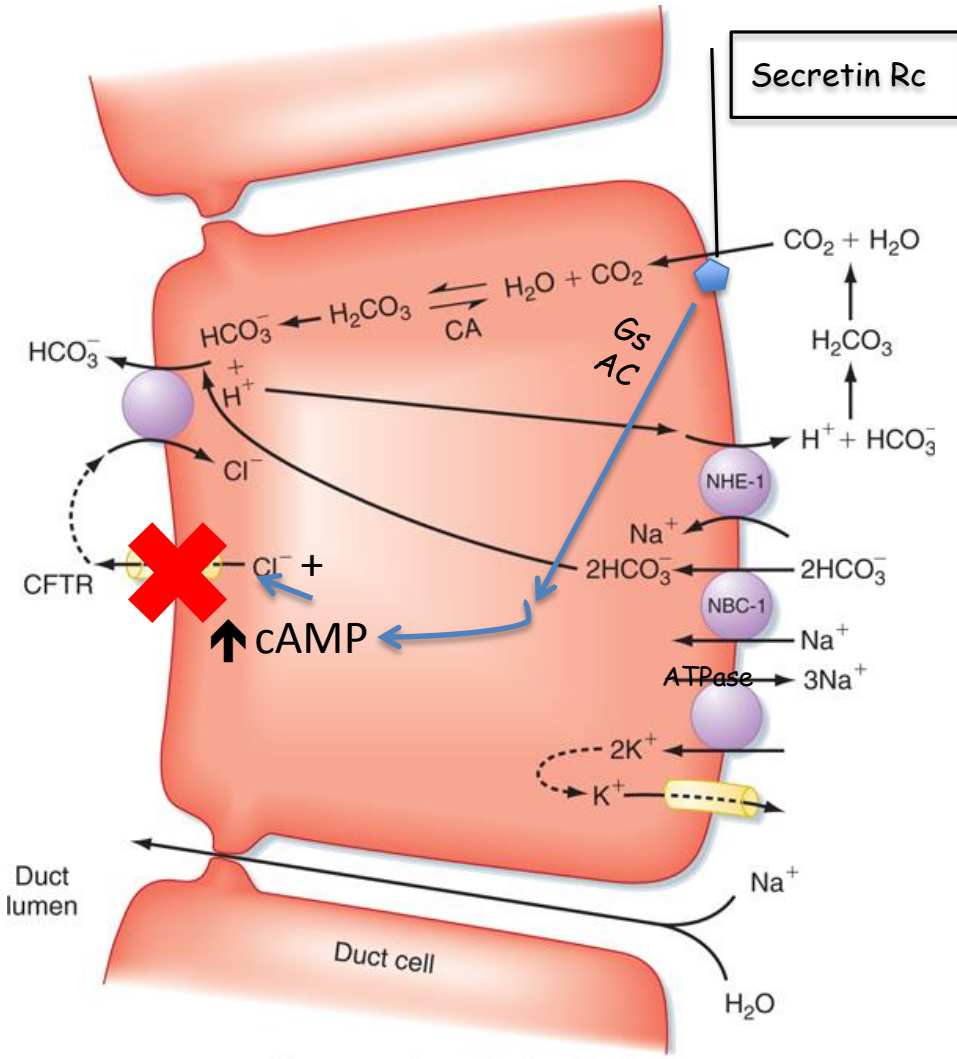
- A top life-limiting genetic disease- 1 in 2000 life Caucasian births
- Defect in the cystic fibrosis transmembrane conductance regulator (CFTR)
- Epithelial dysfunction-- abnormal hydration of secretions in lung, intestine, pancreas, biliary tract, vas deferens, sweat



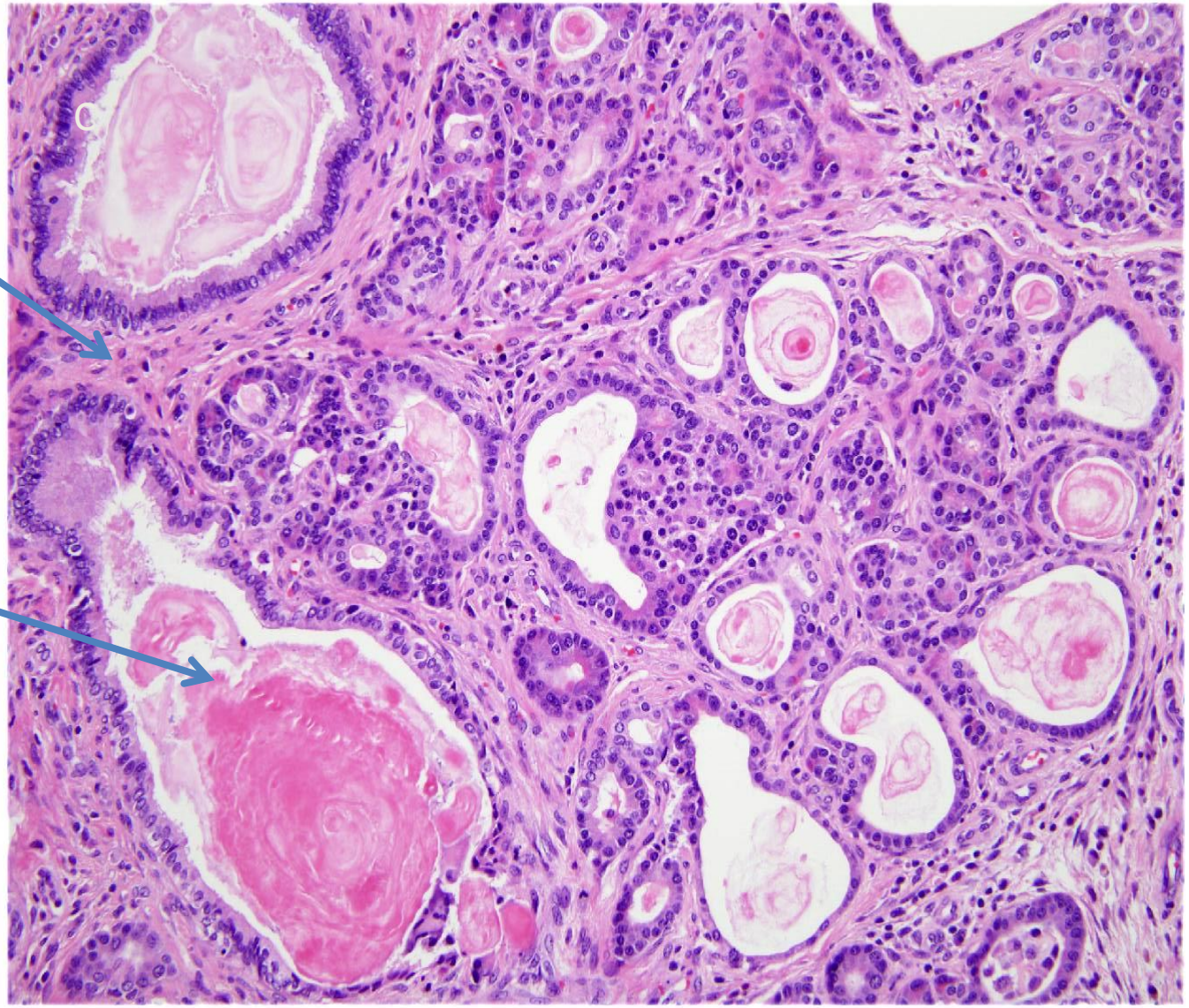
Mechanism for secretion impairment in CF

Pancreatic duct cells

- CFTR conductance critical:
  - Hydration if the luminal proteins (zyomogens)
  - Bicarbonate (base) secretion
- Many patients with CF born with pancreatic insufficiency
  - Blocked ducts
  - Chronic inflammation→fibrosis→ atrophy→exocrine insufficiency
  - Impaired neutralization of stomach acid



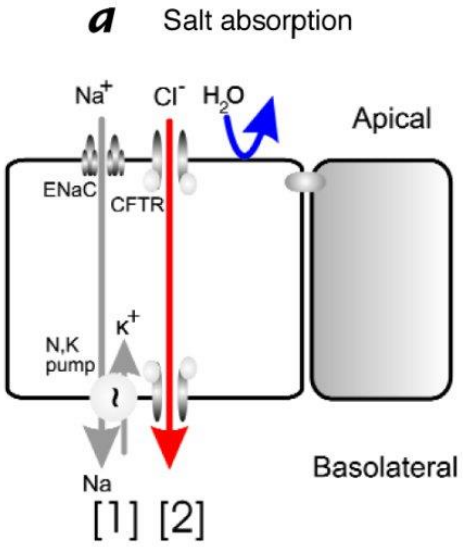
Clinical correlation- Pancreas Explant- Infant with Cystic Fibrosis



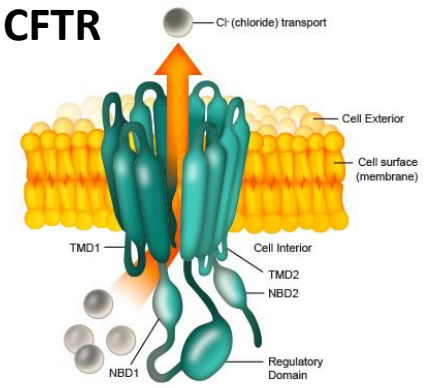
Note bands of fibrosis and mucus inspissation within dilated ducts. Non-hydrated, non-alkaline secretions →→ glandular insufficiency in infancy.

Thought Question about Sweating in CF

- If patients with CF have abnormal CFTR, how is it that the sweat is salty? Isn't there impaired salt and water secretion?



ANSWER: it depends on the mucosa. In sweat gland, apical Na+ moves in via ENaC, while CFTR transports Cl- into cells as counter ion. Mucosa relatively impermeable to water--- thus we can make hypotonic sweat in health.



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http://www.jci.org/articles/view/6222/figure/1

http://www.cftr.info/about-cf/role-of-ctfr-in-cf/genetics-and-cell-biology-of-cftr/cftr-structure-and-regulation/

Organic Components of Pancreatic Juice

Proenzymes	Enzymes
Cationic trypsinogen	Amylase
Anionic trypsinogen	Carboxylesterase
Mesotrypsinogen	Sterol esterase
Chymotrypsinogen A and B	Lipase
Kallireinogen	DNase
Procarboypeptidases A and B	RNase
Proelastase	Pancreatic secretory trypsin inhibitor
Prophospholipase	
Procolipase	

- All **proteases** are secreted in inactive form (zyomogens or proenzymes)
- Enzymes are activated by trypsins in lumen

Activation of Pancreatic Enzymes

KEY POINT: lipase secreted in <u>active</u> form; co-lipase in <u>inactive</u> form

Active Enzyme (pH 7)

Trypsin
Chymotrypsin
Elastase
Carboxypepditase A & B

Co-lipase
Phospholipase A2

Trypsin

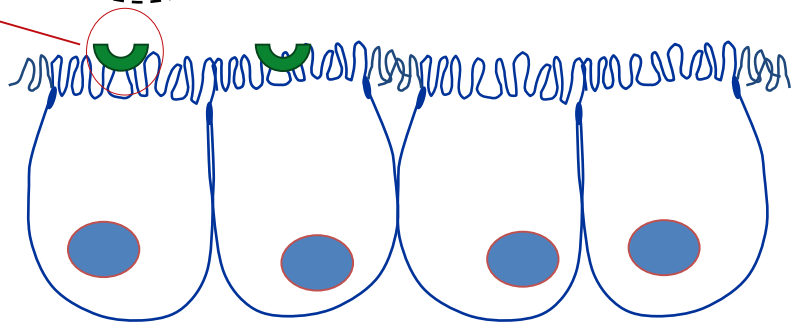
ProEnzyme (Inactive)

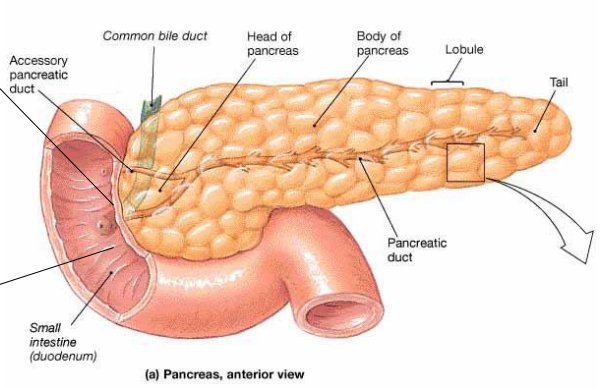
Trypsinogen
Chymotrypsinogen
Proelastase
Procarboxypepditase A & B

Pro-Co-lipase
Pro-phospholipase A2

Trypsinogen

Enterokinase

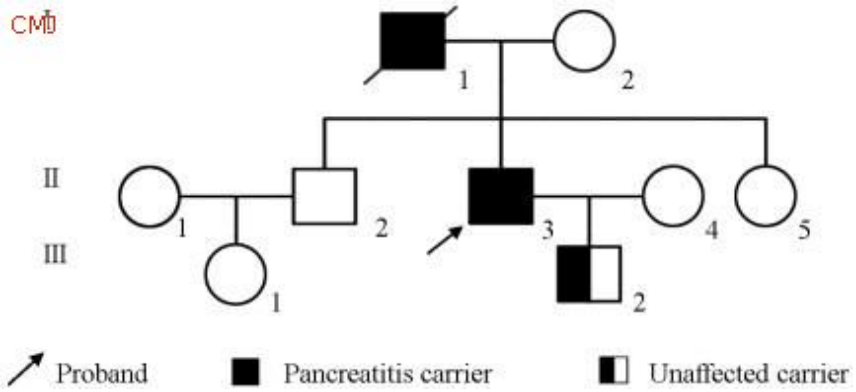




See slide set 'Protein digestion'

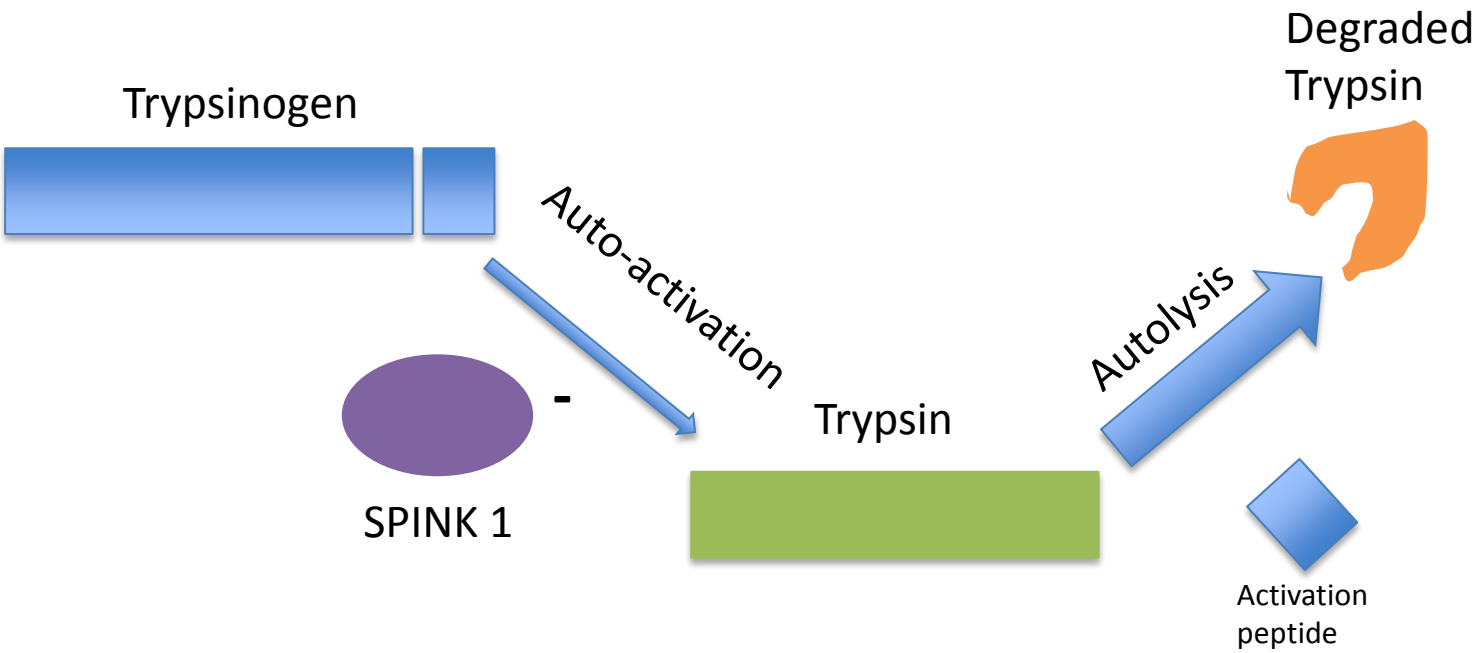
Modified from Dr W Lencer

Clinical Correlation- Hereditary Pancreatitis from PRSS1 mutation



- Encodes cationic trypsinogen
- A common mutation replaces the amino acid arginine with histidine at position 122 (R122H)→ prematurely (within the gland) activated trypsin resistant to degradation.
- Autosomal dominant; penetrance ~ 80%
- Results in repeated episodes of acute and then chronic pancreatitis

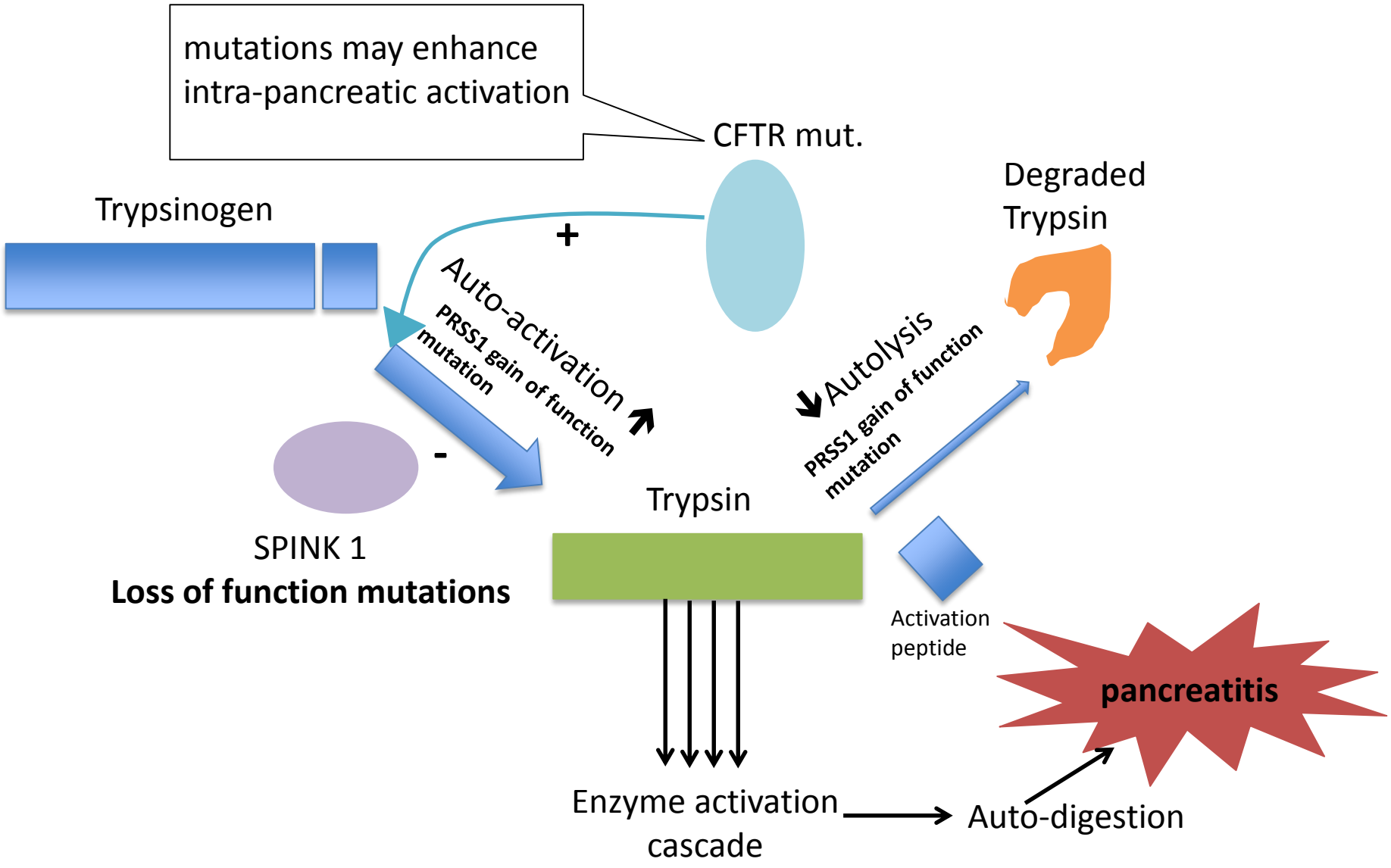
Within the Pancreas…normally



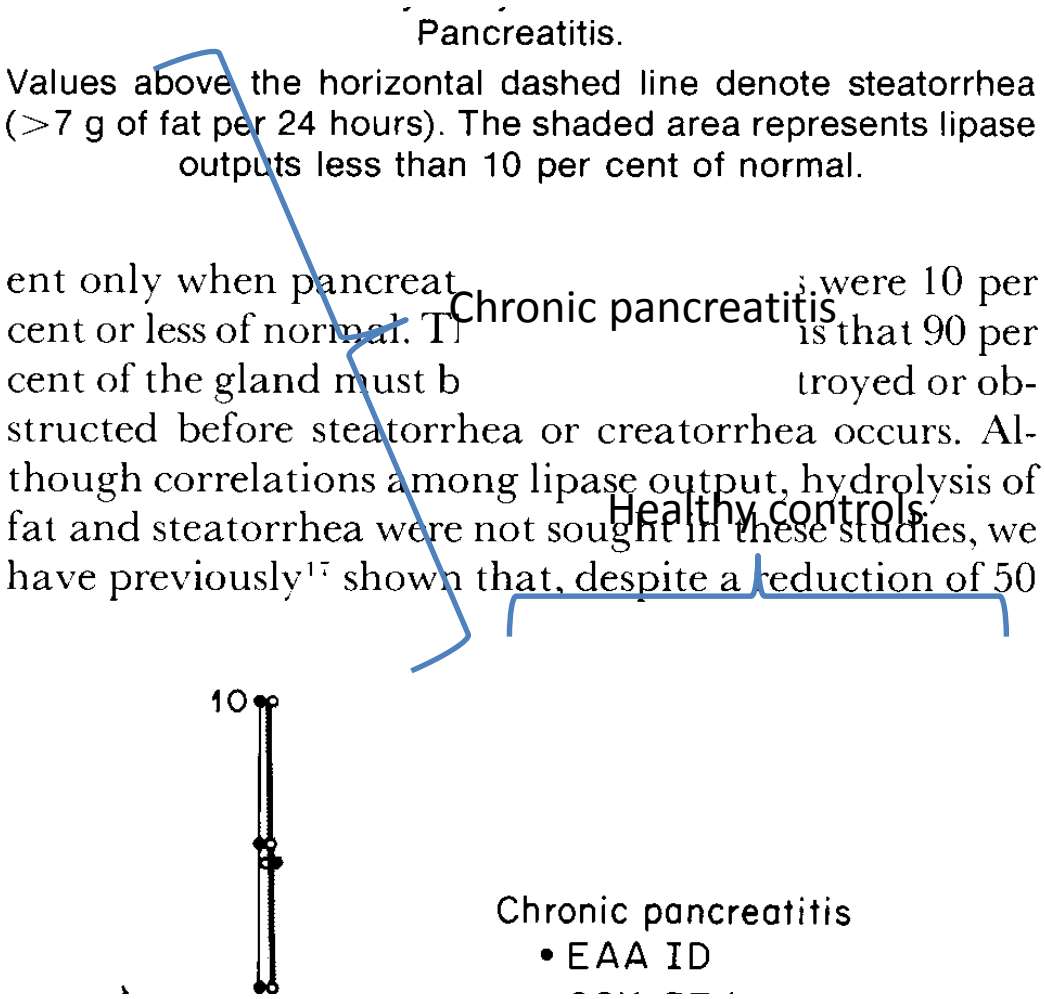
No significant intra-pancreatic digestion

After Witt Gut 2003 52(Suppl II): ii31-ii41

Within the Pancreas…abnormal



Excess Capacity in non-infants

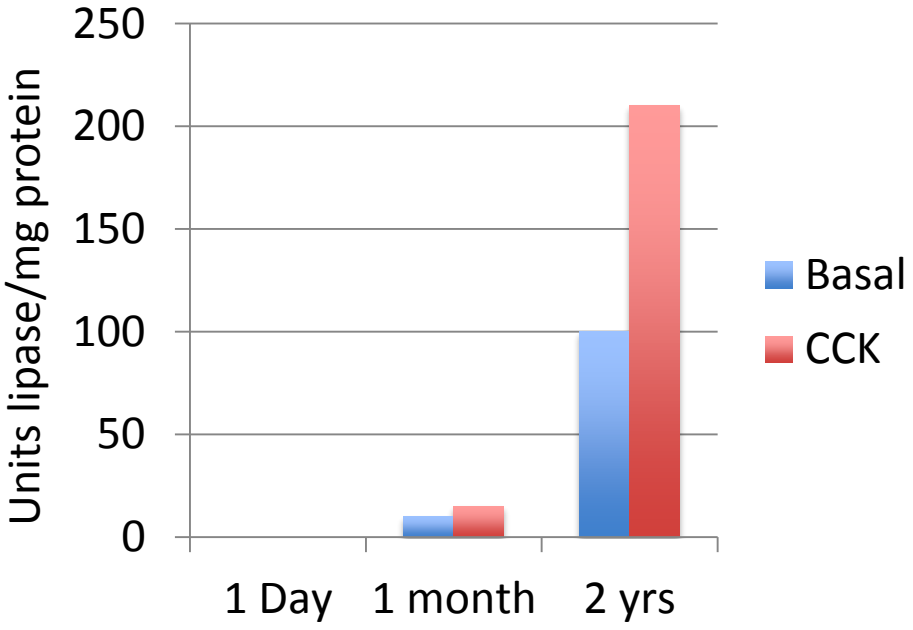


- A study of 17 adults with chronic pancreatitis and 33 healthy controls
- Duodenal intubation to determine lipase production
- Demonstrates the '10%' rule → abnormal fecal fat loss when function <10%

DiMagno et al. NEJM 1973 288: 813-15 (used with permission)

Developmental Pancreatic Insufficiency- starch and fat

- Lipase, amylase secretion low until 2 years of age
- Normal coefficient of fat absorption in infants 80-85% (>95% in older children and adults)
- Compensation: salivary amylase, infant diet, breast milk lipase, gastric/ lingual lipases



Data from Lebenthal and Lee. 1980 Pediatrics 66:556. Basal and CCK stimulated specific activity of lipase in duodenal fluid according to age group.

Thought Question - celiac disease and pancreatic function

On average, patients with untreated celiac disease and villus atrophy have lower pancreatic intraluminal lipase activity as compared to normal or celiac subjects without atrophy.

A. What physiologic problem in the control of pancreatic secretion could explain this difference?
B. Could this difference contribute to abnormal fat digestion?

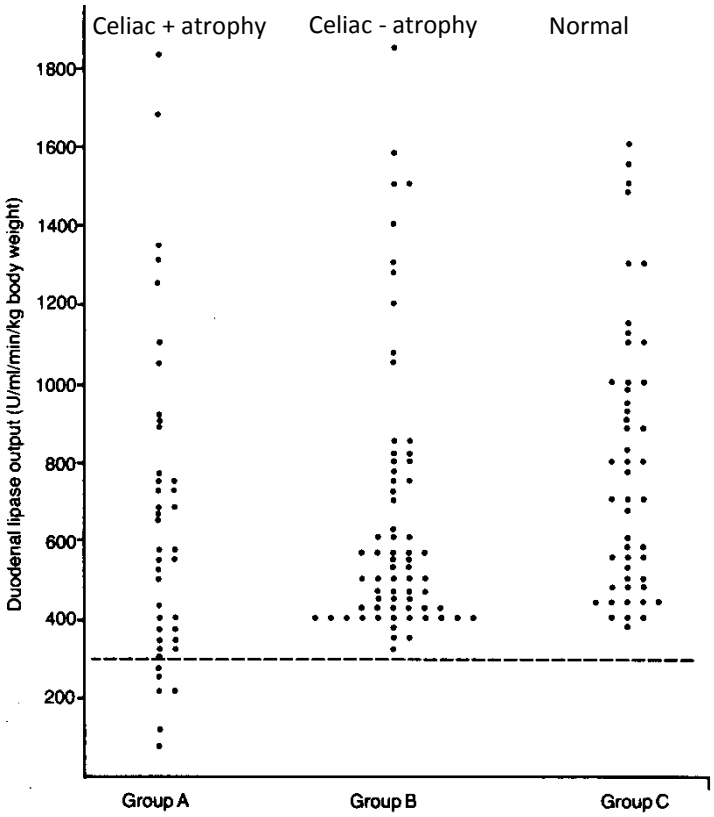


Figure 3: Individual duodenal lipase outputs (in one of two 15 minute samples after secretin+caerulein injection) expressed in units per ml per minute per kg body weight in the three groups. Group A: coeliac patients with total villous atrophy; group B: coeliac patients with normal intestinal villi; group C: control subjects. Dotted line=low normal limit.

Dotted line represents lower limit of 'normal activity'

egg yolk emulsion according to Figarella and Ribeiro[19]; chymotrypsin was assayed on its speci-

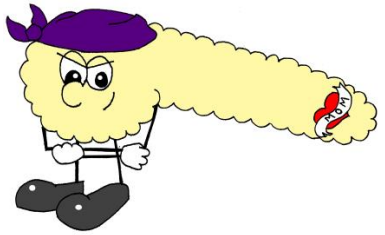
Duodenal lipase activity 15 minutes after fatty meal

Based on Carroccio et al. 1991 (used with permission)

Thought Question - celiac disease and pancreatic function

- A. Simplest answer: mucosal damage has compromised the signaling enteroendocrine cells, resulting in less meal-stimulated production of CCK, and less enzyme release from pancreatic ascinar cells
- B. Unlikely; based on the 10% rule, few/none of the patients in column A have <10% lower limit of normal lipase activity. We presume co-lipase activity is similarly affected.

Summary Pancreatic Secretion



1. Enzymes are secreted from ascinar cells under the influence of CCK.
2. Enzymes are washed into duodenum by bicarbonate rich, chloride poor iso-osmotic fluid under influence of secretin.
3. CCK = 'food sensor' Secretin = 'acid sensor'
4. Proteases and some lipases need to be activated in duodenal lumen- this starts with trypsin.
5. There is excess capacity in the pancreas– recall '10% rule'.
6. Exocrine gland function matures in infancy and results in adult fat absorption by ~ 2- 3 years of age.

http://evictedpancreas.wordpress.com/multimedia/cartoons/ (used with permission)

Boards-style question- Pancreas

- Which of the following statements about control of pancreatic secretion is correct?
  A. Pancreatic enzyme secretion is maximally stimulated by intact protein in the lumen of the duodenum.
  B. All proteases are secreted as inactive ‘pro’ enzymes requiring activation in the duodenal lumen.
  C. Acidic milieu enhances the function of intra-duodenal pancreatic enzymes.
  D. Pancreatic duct cells are maximally stimulated when the duodenal lumen is alkaline.

Please send any questions or comments to:

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