Pancreas

1. An understanding of lumenal digestion
2. Pancreas physiology – regulation of digestive enzyme and bicarbonate secretion
3. Pancreatic pathology

Pancreas; Pancreatitis; lumenal digestion
SECRETION

Salivary Glands
1500 ml

Stomach
2500 ml

Pancreas
1500 ml

Liver
500 ml

Small Intestine
-7500 ml

Large Intestine
-1300 ml

amylase
mucus
bicarbonate

HCl
pepsinogen
intrinsic factor
digestive enzymes
bicarbonate & water
bile

absorption of digestive
products
absorption of water
secretion of water

absorption of water
Pancreas Histology

• Endocrine Pancreas
  – β cells: insulin
  – α cells: glucagon
  – δ cells: somatostatin

• Exocrine Pancreas
  – Acinar cells: digestive enzymes
  – Centroacinar cells
  – Duct cells
Fig. 8a. Pancreatic exocrine cell. (Guinea pig). Distribution of radioautographic grains in specimen fixed at the end of a 3 min. pulse with L-[H-4,5]leucine.

gr, radioautographic grains; n, nucleus; m, mitochondria; zg, zymogen granules; rc, region of the cytoplasm occupied by the rough surfaced endoplasmic reticulum. At this time, ~ 85% of the grains are found associated with such regions.

x 12,000

Fig. 8b. Pancreatic exocrine cell. (Guinea pig). Distribution of radioautographic grains at the end of a 37 min chase (after a 3 min pulse as in Fig. 8a).

cv, condensing vacuoles; zg, zymogen granules; rc, region of the cytoplasm occupied by the rough surfaced endoplasmic reticulum. The periphery of the Golgi complex is marked by arrows. At this time, ~ 50% of the radioautographic grains are associated with condensing vacuoles.

x 12,000

Zymogen granules

- Specialized organelles for regulated secretion
  - Storage and concentration of digestive enzymes
  - Secretion is stimulated
  - Secretion is polarized
Digestive Enzymes

• Serine endopeptidases
  – Trypsin (Arg or Lys)
  – Chymotrypsin (Phe, Tyr, or Trp)
  – Elastase (aliphatic side chains, Val, Gly, Leu)
• Exopeptidases
  – Carboxypeptidase
• Lipase (hydrolysis of C1 and C3 glycerol ester bonds)
• Phospholipase A2 - cleaves C2 ester bond of triglycerides
• Colipase (cofactor for lipase)
NH2-Val-Glu-Arg-Glu-Ala-Tyr-Gly-Trp-Met-Asp-Gln-COOH

Trypsin →

carboxypeptidase

carboxypeptidase →

chymotrypsin
• Amylase (hydrolysis of $\alpha_1,4$-glycosidic bonds in starches)
• Ribonuclease - hydrolysis of phosphate bonds in RNA
• Deoxyribonuclease - hydrolysis of phosphate bonds in DNA
Regulation of Acinar Cell Secretion

- Cholecystokinin
- Acetylcholine
- Secretin
  - Much less potent than CCK and Ach
Figure 2. Human pancreatic acini secrete amylase in response to carbachol but not to CCK-8 or gastrin. Isolated human pancreatic acini, either uninfected or infected for 4 hours with an adenovirus expressing the human CCK-B receptor, were incubated with increasing concentrations of CCK-8, gastrin, or carbachol at 37°C for 30 minutes. The concentration of amylase released into the medium was measured using colorimetric reagent and was expressed as a percentage of initial acinar amylase content. Data are means of 3 separate experiments.
FIG. 18. Schematic diagram illustrating the histology of a functional unit of the pancreas.
Secretin

- Stimulation of pancreatic water and bicarbonate secretion
- Potentiates the action of CCK/Ach in stimulating pancreatic enzyme secretion
Secretin

• Secretin secretion is stimulated by
  – acidification of the duodenum
  – products of fat digestion
Fig. 9-5. Pancreatic bicarbonate output in response to various duodenal pH values. The output of bicarbonate is used as an index of secretin release.
Zollinger-Ellison Syndrome

- Gastrin secreting tumors
- Multiple ulcerations
  - Gastrointestinal bleeding common
- Malabsorption- WHY?
Zollinger-Ellison Syndrome

- Gastrin secreting tumors
- Multiple ulcerations
  - Gastrointestinal bleeding common
- Malabsorption - high acid secretion overpowers the ability of pancreatic bicarbonate to neutralize the intestinal content.
Why doesn’t the pancreas digest itself?
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- digestive enzymes are stored within membrane-bound organelles as inactive precursors
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- digestive enzymes are stored within membrane-bound organelles as inactive precursors
- the digestive enzymes are activated at a distant site within the intestinal lumen
Trypsin Activation Represents the Key Step

![Diagram showing the activation of trypsin from trypsinogen through the actions of enterokinase and various zymogens and enzymes.](Image)
Trypsinogen

Green = propeptide

Trypsin

orange = inhibitor
Enteropeptidase Deficiency (enterokinase)

- Enteropeptidase is present in intestinal brush border membranes.
- Presents in children as life threatening intestinal malabsorption.
- Corrected with the administration of pancreatic enzymes
Why doesn’t the pancreas digest itself?

- digestive enzymes are stored within membrane-bound organelles as inactive precursors
- the digestive enzymes are activated at a distant site within the intestinal lumen
- intracellular mechanisms exists to compensate for trypsinogen that is activated within the pancreas
Intracellular Protective mechanisms

• **SPINK1** (PSTI) - pancreatic secretory trypsin inhibitor
  – binds to activated trypsin as a substrate
  – with time, catalysis occurs and activated trypsin is released

• **mesotrypsinogen and enzyme Y**
  – activated by trypsin
  – degrades cationic trypsin, chymotrypsin, and elastase
  – resistant to SPINK1 (PSTI) inhibition
a) normal pancreas

b) chronic pancreatitis

- trypsinogen
- mesotrypsin
- trypsin
- SPINK1
- enzyme cascade
- autodigestion

In chronic pancreatitis, there is a lack of SPINK1 activity, leading to the activation of trypsin and triggering an enzyme cascade, which results in autodigestion and pancreatitis.
Hereditary Pancreatitis

- Autosomal dominant
- ~80% penetrance
- mean age onset of symptoms ~14
- Cumulative risk of pancreatic cancer: 40-75%
Fig. 1a, Partial pedigree of one of the HP kindreds. The integers below the boxes are laboratory accession numbers which correspond with the electropherograms in panel b.

b, DNA sequencing electropherograms, aligned with the pedigree in the top panel, showing the DNA sequence of the human cationic trypsinogen gene in the region of the HP mutation. Specimens from HP affected family members (14199 & 13055) and an obligate carrier family member (12982) demonstrate heterozygosity at the fifth nucleotide in the frame (see arrows in the 2nd, 4th, and 5th panels). The sequencing signal is almost exactly 50% G and 50% A for each of these three specimens. In contrast, the signal observed for the two unaffected family members (14935 & 14893) is 100% G which is in keeping with the published sequence for cationic trypsinogen. All DNA amplifications and sequencing were performed as described\textsuperscript{11,12}.
Acute Pancreatitis

• responsible for ~100,000 admissions/year
• ~2,500 deaths/year
Acute Pancreatitis

Etiology

• gallstone disease (45%)
• alcohol (35%)
• other (20%) - immunosuppressives, Coxsackie B, mumps, scorpion bites, trauma, genetics, etc.
“Edematous” and “Hemorrhagic” Pancreatitis
Normal Pancreas
Acute Pancreatitis
Normal Pancreas

Figure 1. Normal pancreas. A, Pancreas is sharply defined, is homogeneous in density, and has an acinar configuration (arrows). B, Uncinate process has a similar texture (arrow). It is located medial to duodenum (d) and anterior to IVC (V). Peripancreatic fatty tissue is homogeneously low in density. CT scan performed because of abdominal pain and hyperamylasemia. Grade A staging.
Amylase 1400 IU, grade A, no necrosis, CT severity index = 0
grade E, necrosis > 50%, CT severity index = 9
Subsequent pseudocyst formation
Chronic Pancreatitis

- Decline in digestive enzyme secretion from the acinar cells
- Decline in bicarbonate secretion from the ducts
- Characterized by inflammation, fibrosis, and acinar cell dropout
Chronic Pancreatitis

• 85% have a history of alcohol abuse
• Other causes: cystic fibrosis, hereditary pancreatitis with mutations in cationic trypsinogen or SPINK1 (PSTI)
Pancreatic Acinar Atrophy
Chronic Pancreatitis - Atrophy
Complications of Pancreatitis

- Pleural effusions
- Pancreatic pseudocyst
- Diabetes
- Pain from perineural fibrosis
- Pancreatic calcification
- Ascites
- Stones in pancreatic duct
- Fat malabsorption (steatorrhea, ↓ vitamin K)
Pancreatic Pseudocyst
Secretin stimulation test

- Response to secretin administration is used to test for pancreatic function
  - Secretin stimulation test: measure total amount of bicarbonate secreted
  - MRI scan with secretin stimulation: measure change in duct size with secretin stimulation
72 hour fecal fat exam

- Ingest a 100 gram fat diet
- Collect your stools for 72 hours
- Measure the volume of stool and the fat content
Chronic Pancreatitis-Treatment

• Administration of digestive enzymes with meals
  – Antacids are administered with the enzymes
    (e.g. Baking soda - sodium bicarbonate)
Cystic Fibrosis

- Heterozygotes for CFTR mutations is associated with idiopathic acute and chronic pancreatitis

- CFTR mutation incidence is 1/2000 live Caucasian live births
Cystic Fibrosis

- 80% of patients with CF who harbor the classic F508 deletion will have severe pancreatic disease
- Pancreatic duct obstruction is common
- Progressive pancreatic fibrosis
- Secretions are often acidic
Findings on Endoscopic Retrograde Cholangiopancreatography and Ultrasonography (Insets) in a 72-Year-Old Woman with Sclerosing Pancreatitis