Exocrine Pancreatic Function

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Master’s Course in Gastroenterology

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A union of the pancreatic duct and the common bile duct
The pancreas, one of the most important organs involved in the assimilation of food

**Endocrine function:** Secretes hormones
Regulates metabolism
Islets of Langerhans at the highest concentration at the tail

**Exocrine function:** Secretes digestive enzymes and bicarbonate (humans: 1 L of pancreatic juice daily consisting of water, electrolytes and digestive enzymes)
Affects digestion and absorption of nutrients
Clusters of acini (>8% of the pancreas)
Pancreatic Endocrine Function

Secretes hormones: insulin, glucagon, somatostatin
  • alpha cells – secrete glucagon
  • beta cells – secrete insulin
  • delta cells – secrete somatostatin
  • gamma (or PP) cells – secrete pancreatic polypeptide
Pancreatic Exocrine Function

Exocrine portion synthesizes and secretes digestive enzymes and bicarbonate within acini. Production of enzymes occurs in great excess.
**Acinar**

- Synthesize and secrete enzymes
- Receptors for neurohumoral agents at the basolateral site involved in stimulus secretion coupling
- Zymogen granules (containing enzymes) at the apical site
- Following stimulation granules undergo exocytosis at the apical site

**Ductular ( centroacinar)**

- Classical epithelial cells with tight junctions that control passive permeability
- Transport bicarbonate ions into pancreatic juice in lumen of duct
- Water follows paracellularly along the osmotic gradient
- Dilutes pancreatic juice and makes it alkaline (pH 8.3)
The pancreatic acini drain into pancreatic ductules and then the duct
Postprandial pancreatic secretion is mainly ascribed to the gut hormones secretin and cholecystokinin CCK in addition to vagovagal reflexes.
Secretin

- Stimulates pancreatic juice and HCO₃⁻ secretion by ductular cells (in addition to gastric acid secretion and gastric motility).
- Stimulus: low pH after a meal
- Its discovery initiated the field of Endocrinology: Bayliss and Starling in 1902
  - A loop of jejunum was enervated in an anaesthetized dog such that it was connected to rest of the body only by blood vessels. When acid was infused into the lumen of the isolated jejunum, pancreatic secretion occurred.
- Synthesized by S cells in crypts from duodenum
- Binds to its receptor expressed in the pancreas, stomach, liver, kidney, colon, heart, lung, ovary, and brain.
- In the pancreas, secretin receptor is present in both the ductular and acinar cells on the basolateral site
Cholecystokinin (CCK)

- Stimulates pancreatic enzyme secretion
- Released by hydrolytic products of digestion such as amino acids and fatty acids
  - Plasma concentrations: Fasting: 1 pmol/L; 30 min after ingestion of a meal rich in protein and fat: 6-8 pmol/L; In the ensuing 3 h: gradual decline to baseline
- Synthesized in the upper jejunum
- CCK1R receptor “alimentary” expressed on pancreatic acini and abdominal branches of the vagus nerve; binds sulfated CCK
- CCK2R receptor “brain” expressed in the brain; binds gastrin and CCK (sulfated and nonsulfated).
- Direct functional responses of CCK1R to CCK were never characterized
- The vagovagal reflex plays an important role: major effects of CCK on pancreatic secretion are mediated by receptors on vagus nerve, even in species that bear CCK1R on pancreatic acinar cells
Vagovagal reflexes

Feeding stimulates neural mechanisms:

1. Small cephalic phase mediated by vagus
2. Passage of chyme from stomach to duodenum: vagal reflexes
3. Acetylcholine (neurotransmitter) released by vagus directly stimulates acinar cells
• Primary stimulus: Secretin

• cAMP increase → activates protein kinase A → phosphorylates CFTR
• Cl⁻ exchanges for bicarbonate via exchanger
1. Receptors for vasoactive intestinal polypeptide (VIP) and secretin

- Activate G protein to activate adenylate cyclase (AC) that leads to cAMP
- cAMP activates protein kinase A (PK-A)

2. Receptors for bombesin, CCK and acetylcholine (ACh) – dominant pathway

- Activate G proteins to activate phospholipase C (PLC)
- PLC hydrolyzes phosphatidylinositol 4,5-biphosphate (PI-P2) to inositol 1,4,5-triphosphate (IP3) and diacylglycerol (DAG)
- IP3 releases Ca\(^{2+}\) from the ER: Ca\(^{2+}\) influx across the plasma membrane
- Ca\(^{2+}\) binds to calmodulin (CAM) which activates several protein kinases and one protein phosphatase
- DAG and Ca\(^{2+}\) activate protein kinases C
## Pancreatic Digestive Enzymes

### Table 4-1. Pancreatic Acinar Cell Secretory Products

<table>
<thead>
<tr>
<th>Proteases</th>
<th>Amylolytic enzyme</th>
<th>Lipases</th>
<th>Nucleases</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trypsinogen*</td>
<td>Amylase</td>
<td>Lipase</td>
<td>Deoxyribonuclease</td>
<td>Procolipase*</td>
</tr>
<tr>
<td>Chymotrypsinogen*</td>
<td>Nonspecific esterase</td>
<td>Ribonuclease</td>
<td></td>
<td>Trypsin inhibitors</td>
</tr>
<tr>
<td>Proelastase*</td>
<td>Prophospholipase A₂*</td>
<td></td>
<td></td>
<td>Monitor peptide</td>
</tr>
<tr>
<td>Procarboxypeptidase A*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procarboxypeptidase B*</td>
<td></td>
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</tr>
</tbody>
</table>

*Stored and secreted in inactive forms.

- Acts to inhibit trypsin if it is prematurely activated

- ~80% of weight of proteins secreted are proteases

- ~40% of weight of proteins secreted is trypsinogen
Activation of Pancreatic Enzymes

Procarboxypeptidase (inactive) → Carboxypeptidase
Chymotrypsinogen (inactive) → Chymotrypsin (active)
Trypsinogen (inactive) → Trypsin

Membrane-bound enterokinase

Intestinal lumen
Overview Digestive Enzymes

**Path of absorption**

**Carbohydrate digestion**

**Absorption:** The monosaccharides glucose and galactose are absorbed via cotransport with sodium ions; fructose passes via facilitated diffusion. All monosaccharides enter the capillary blood in the villi and are transported to the liver via the hepatic portal vein.

**Protein digestion**

**Absorption:** Amino acids are absorbed via cotransport with sodium ions; they enter the capillary blood in the villi and are transported to the liver via the hepatic portal vein.

**Foodstuff**

- **Starch and disaccharides**
  - Salivary amylase
  - Pancreatic amylase

- **Oligosaccharides and disaccharides**
  - Lactose
  - Maltose
  - Sucrose
    - Brush border enzymes in small intestine (dextrinase, glucoamylase, lactase, maltase, and sucrase)

- **Lactose**
  - Galactose
  - Glucose
  - Fructose

- **Protein**
  - Pepsin (stomach glands) in the presence of HCl

- **Large polypeptides**
  - Pancreatic enzymes (trypsin, chymotrypsin, carboxypeptidase)

- **Small polypeptides, small peptides**
  - Brush border enzymes (aminopeptidases, carboxypeptidase, and dipeptidases)

- **Amino acids** (some dipeptides and tripeptides)

**Site of action**

- **Mouth**
- **Small intestine**
- **Stomach**
- **Small intestine**
Overview Digestive Enzymes

Path of absorption

Fat digestion

Absorption: Fatty acids and monoglycerides enter the intestinal cells via diffusion. They are combined with proteins within the cells, and the resulting chylomicrons are extruded. They enter the lacteals of the villi and are transported to the systemic circulation via the lymph in the thoracic duct. (Glycerol and short-chain fatty acids are absorbed into the capillary blood in the villi and transported to the liver via the hepatic portal vein.)

Nucleic acid digestion

Absorption: Active transport via membrane carriers; absorbed into capillary blood in the villi and transported to the liver via the hepatic portal vein.

Foodstuff

Unemulsified fats

- Emulsified by the detergent action of bile salts ducted in from the liver
- Pancreatic lipase

Monoglycerides and fatty acids

Glycerol and fatty acids

Enzyme(s) and source

Site of action

Small intestine

Small intestine

Nucleic acids

- Pancreatic ribonuclease and deoxyribonuclease
- Brush border enzymes (nucleosidases and phosphatases)

Pentose sugars, N-containing bases, phosphate ions.
Chronic Pancreatitis
TIGAR-O Classification

- Toxic-metabolic
  - Alcohol (70-80%), tobacco, hyperglycemia, hyperlipidemia, chronic renal failure, medication (Phenacetin)
- Idiopathic (15%)
  - Early onset, late onset, tropical (chronic hypercalcemia)
- Genetic
  - Mutation in trypsinogen or CFTR
- Autoimmune (primary biliary cirrhosis, Sjögren’s syndrome, IBD)
- Recurrent and severe acute pancreatitis
  - Necrosis-fibrosis
- Obstruktive
Acinar cell hyperactivity
- Secretion pancreatic juice with imbalanced pancreatic stone promoters and inhibitors
- Leads to protein plug formation

Acinar cell atrophy
- Ectasia (dilation or distention of ducts)
- Intraductal stones
Cystic Fibrosis

Cystic fibrosis is the commonest inherited pancreatic disorder
Autosomal recessive disorder

Defect in cAMP-regulated membrane Cl\textsuperscript{−} conductance in epithelial cells: defective secretion of HCO\textsubscript{3}{\textsuperscript{−}} in pancreas.

Abnormality of the CF gene affects the cystic fibrosis transmembrane conductance regulator located at the apical domain of ductular cells.

fluid secretion and alkalinization
Clinical signs

Defective dilution and alkalinization of exocrine secretions, including those in pancreatic ducts, bile ducts, bronchial epithelium, and sweat glands.

- Abnormally viscosity of exocrine secretions and increased electrolyte concentrations in sweat and saliva.

- Consequences:
  - intrauterine growth retardation
  - impaired foetal development
  - obstruction of the neonatal gut
  - recurrent respiratory infection
  - Bronchiectasis
  - chronic obstructive pulmonary disease
  - focal biliary cirrhosis
  - pancreatic exocrine insufficiency
  - male genital tract lesions in the ductal systems

- The pancreas is small and irregular. Dilatation of ducts, enzyme leaks, and cycles of autodigestion lead to fat, fibrosis, and cystic changes, eventually impairing pancreatic islet function.

- Diarrhoea and steatorrhoea are the most common gastroenterological findings.
Diagnosis

Laboratory and special examinations:
- increased sweat Na$^+$ and Cl$^-$ concentrations
- molecular genetic methods: CFTR mutations
- Steatorrhoea may be demonstrated by analysis of stool fat
- Imaging: ultrasound, CT and ERCP

Prognosis

With improving attention to respiratory complications, median survival has increased to 29 years. Some patients survive to the fifth decade. The most critical factor is to prevent dehydration and infectious respiratory events.
Exocrine pancreatic tumours

A primary adenocarcinoma originating in pancreatic cells (excluding endocrine elements)
Most pancreatic adenocarcinomas produce mucin (75%) and are located in the head of the pancreas.
The tumours frequently extend to the retroperitoneum or invade adjacent organs, such as the stomach, duodenum, or gallbladder.

Tumours mostly originate from pancreatic ducts (88%)

Diagnosis and staging
Imaging studies are most helpful
In patients unfit for major pancreatic resection, the diagnosis is frequently with transabdominal ultrasound or CT (sensitivity and specificity 80%).
ERCP has sensitivity and specificity of 90%, and offers the opportunity for palliation in those with obstructive jaundice.
Only 10% of tumours are resectable.
Palliation
- For the majority of patients, palliation rather than cure.
- Palliative surgery may be necessary for biliary or gastrointestinal obstruction.

Whipple procedure
- Removal of the distal half of the stomach, the gall bladder and its cystic duct, the common bile duct, the head of the pancreas, duodenum, proximal jejunum and regional lymph nodes.
- Reconstruction consists of attaching the pancreas to the jejunum and attaching the hepatic duct to the jejunum to allow digestive juices and bile to flow into the gastrointestinal tract and attaching the stomach to the jejunum to allow food to pass through.
- Exocrine pancreatic insufficiency may require pancreatic enzyme replacement.
An expandable stent, seen from the papilla of the duodenum, emerging from the bile duct where it is stenting an obstruction due to carcinoma of the pancreas.
ERCP

- Access to papilla by guided wire
- Sphincterotomy