Gastric and Pancreatic Secretion

Outline

GASTRIC FUNCTION
• Products secreted by stomach. Composition of gastric juice
• Acid secretion
  ✓ Parietal cell function, H-K pump
  ✓ Secretagogues
  ✓ Regulation
  ✓ Response to a meal
• Pepsinogen secretion
• Protection of gastric surface & acid neutralization

PANCREATIC FUNCTION
• Products secreted by pancreas. Composition of pancreatic juice
• Pancreatic acinar cell function & regulation
• Pancreatic duct cell function & regulation
• Response to a meal
Anatomy of the stomach: cardia, corpus, antrum

Fig 42-1  p. 864
Secretory rate affects composition of gastric juice

Secretions at rest: Na⁺ rich basal solution
Stimulated: nearly pure isotonic HCl solution

Maximal acid output
MAO $\sim 10 - 25$ mEq/hr

Basal acid output
BAO $< 5$ mEq/hr

$\frac{BAO}{MAO} = 0.3$ to $0.6$

Fig 42-2  p. 864
Secretions of stomach

Proximal portion of the stomach secretes acid, pepsinogens, intrinsic factor, bicarbonate, and mucus

Distal portion of the stomach releases gastrin and somatostatin

Cell types of stomach

Corpus:
Parietal cells = oxyntic cells
Chief cells = peptic cells
Mucus-secreting cells
Endocrine cells, e.g. enterochromaffin-like cell = ECL cell

Antrum:
Chief cells = peptic cells
Endocrine cells (G cells [gastrin] and D cells [somatostatin])
Parietal cell: resting & stimulated

secretes both acid and intrinsic factor

Upon stimulation vesicles translocate to the apical cell surface, fuse with the plasma membrane, forming a deeply invaginated apical plasma membrane referred to as the secretory canaliculus

Fig 42-23  p. 865
Acid secretion by the parietal cell

Apical H-K pump (P$_2$-type ATPase)
Inhibitors of H-K pump:
- PPI: omeprazole covalently binds to cysteines
- P-CAB: potassium competitive acid blocker Schering 28080

Recycling of K$^+$ through apical K channels KvLQT1

Secretion of Cl$^-$
Passive through CFTR

Exit of HCO$_3^-$
Basolateral via AE2

Fig 42-4  p. 866
Direct and indirect actions of the 3 acid secretagogues:

- Acetylcholine
- Histamine
- Gastrin

<table>
<thead>
<tr>
<th>Secretagogue</th>
<th>Receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcholine</td>
<td>$M_3$ receptor</td>
</tr>
<tr>
<td>Histamine</td>
<td>$H_2$ receptor</td>
</tr>
<tr>
<td>Gastrin</td>
<td>$CCK_2$ receptor</td>
</tr>
</tbody>
</table>

In the direct pathway, acetylcholine, gastrin, and histamine stimulate the parietal cell, triggering the secretion of $H^+$ into the lumen.

In the indirect pathway, acetylcholine and gastrin also stimulate the ECL cell, resulting in secretion of histamine. This histamine then acts on the parietal cell.

Fig 42-5  p. 867
Receptors & signal transduction of 3 acid secretagogues & inhibitors: Ca\(^{++}\)/diacylglycerol or cAMP
Structure of Gastrin & Cholecystokinin

Single 101-amino-acid protein is processed to both

G-17 (little gastrin) and G-34 (big gastrin)
N-terminal is modified to a pyroglutamyl residue
C-terminal phenylalanine is amidated
Antral G cells release mostly G-17, Duodenal G cells release mostly G-34

Final 5 residues of CCK are identical to those of G-17 and G-34

Fig 42-7  p. 868
Regulation of acid secretion

- Vagal nerve endings release acetylcholine (ACh), and gastrin-releasing peptide (GRP)
- G cells in antrum and duodenum release gastrin
- ECL cells in stomach corpus release histamine
- D cells in stomach antrum and corpus release somatostatin (2 forms: SS-28 and SS-14 with identical C-termini)
Regulation of acid secretion

Fig 42-8  p. 869
Negative feedback from duodenum & jejunum:
fat, acid & hyperosmolar solutions inhibit gastric H\(^+\) secretion

Is there an “enterogastrone?”

Enteric hormones that inhibit gastric H\(^+\) secretion:

<table>
<thead>
<tr>
<th>HORM ONE</th>
<th>SOURCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCK</td>
<td>I cells of duodenum and jejunum and neurons in ileum and colon</td>
</tr>
<tr>
<td>Secretin</td>
<td>S cells in small intestine</td>
</tr>
<tr>
<td>VIP</td>
<td>ENS neurons</td>
</tr>
<tr>
<td>GIP</td>
<td>K cells in duodenum and jejunum</td>
</tr>
<tr>
<td>Neurotensin</td>
<td>Endocrine cells in ileum</td>
</tr>
<tr>
<td>Peptide YY</td>
<td>Endocrine cells in ileum and colon</td>
</tr>
<tr>
<td>Somatostatin</td>
<td>D cells of stomach and duodenum, (\delta) cells of pancreatic islets</td>
</tr>
</tbody>
</table>

Primary role for secretin released by S cells in response to acid
Effect of food intake on acid secretion

**Fig 42-9  p. 871**
Interdigestive phase of gastric acid secretion

(a) Basal state
(b) Accounts for ~ 20 % of acid secretion
Cephalic phase of gastric acid secretion

1. Accounts for 30% of acid secretion

2. Stimulated by the sight, smell, taste, or thought of food, swallowing of food

3. Sensory stimuli activate dorsal motor nucleus of vagus → stimulate parasympathetic preganglionic fibers (vagus)

4. Vagus causes
   a) ACh release on parietal cell → acid secretion
   b) ACh release in lamina propria → stimulates ECL → histamine release
   c) GRP release in antrum → gastrin release from G cells
   d) ACh release → inhibit D cells → less somatostatin release
Gastric phase of gastric acid secretion accounts for 50% of acid secretion

Fig 42-10 p. 872
Intestinal phase of gastric acid secretion accounts for 5% of acid secretion.

Enter-oxyntin = a nongastrin, enteric substance. Not demonstrated in humans.
Activation of pepsinogens to pepsin

Cleavage of N-terminal peptide

Fig 42-12  p. 873
Stimulation of Chief Cells to secrete Pepsinogen

Agonists acting via cAMP

• Secretin receptors
• VIP receptors
• $\beta_2$ adrenergic receptors
• EP$_2$ receptors for PGE$_2$

Agonists acting via Ca$^{++}$

• M$_3$ muscarinic receptors for ACh
• Gastrin/CCK receptors CCK1
Diffusion barrier on the surface of the gastric mucosa

Mucins secreted by
Surface mucous cells
Mucous neck cells
Glandular mucous cells

HCO$_3^-$ secreted by surface cells

Mucins form mucous gel layer with phospholipids, electrolytes & water

Viscous fingering of HCl through mucous layer

Fig 42-13  p. 875
Pancreatic Acinus and Duct Morphology

Fig 43-1 p. 880
Movement of synthesized proteins through secretory pathway
Pancreatic Secretagogues & Amylase Secretion

CCK = cholecystokinin = pancreozymin
GRP = gastrin releasing peptide
VIP = vasoactive intestinal peptide
CGRP = calcitonin-gene-related peptide
Carbachol = muscarinic receptor agonist

Fig 43-3 p. 882
Receptors on basolateral membrane of pancreatic acinar cell

- M₃ muscarinic receptor (CHRM3) for acetylcholine (ACh)
- CCK₁ receptor (CCK1R) with affinity for CCK >> gastrin
- CCK₂ receptor (CCK2R) with affinity for CCK = gastrin
- GRP receptor (GRPR) for gastrin-releasing peptide
- CGRP receptor (CALCRL+RAMP1) for calcitonin-gene-related peptide
- Insulin receptor (INSR) for insulin
- Secretin receptor (SCTR) for secretin
- Somatostatin receptor (SST₁ to 5) for somatostatin (SS)
- VIP receptor (VIPR) for vasoactive intestinal peptide (VIP)

Gene names shown in green
Protein Secretion by Pancreatic Acinar Cell

Altered phosphorylation of structural and regulatory proteins leads to insertion of vesicles (zymogen granules) and thus protein secretion.

Fig 43-4 p. 883
Isotonic NaCl Secretion by Pancreatic Acinar Cell

The movement of Cl⁻ into the lumen makes the transepithelial voltage more lumen negative, driving Na⁺ into the lumen via the tight junctions.

The Na–K pump creates the inwardly directed Na⁺ gradient across the basolateral membrane.

The Na/K/Cl cotransporter produces the net Cl⁻ uptake, driven by the Na⁺ gradient, which is generated by the Na–K pump.

The rise in intracellular [K⁺] that results from the activity of the pump and cotransporter is shunted by basolateral K⁺ channels that provide an exit pathway for K⁺.

The intracellular accumulation of Cl⁻ establishes the electrochemical gradient that drives Cl⁻ secretion into the acinar lumen through apical membrane Cl⁻ channels.

The hormone CCK and the cholinergic neurotransmitter acetylcholine are potent stimulators of Cl⁻ secretion.

Fig 43-5 p. 884
Bicarbonate Secretion by Pancreatic Duct Cell

1. Bicarbonate secretion into the lumen occurs via Cl-2HCO₃⁻ exchange and possibly also Cl⁻ channels.
2. Some of the HCO₃⁻ that enters the lumen directly enters the cell across the basolateral membrane via an Na/HCO₃⁻ cotransporter.
3. Additional intracellular HCO₃⁻ is generated by the activity of cytoplasmic carbonic anhydrase (CA), which catalyzes the formation of HCO₃⁻ from CO₂ and OH⁻.
4. The OH⁻ needed by the CA arises from splitting of H₂O. This reaction is driven by the extrusion of H⁺ by both an Na–H exchanger and an H⁺ pump.
5. The lumen-negative voltage pulls Na⁺ into the lumen, via the tight junctions.

ACh also stimulates HCO₃⁻ secretion. ACh activates Gₛ, which in turn stimulates PLC to release DAG (which stimulates PKC) and IP₃ (which releases Ca²⁺ from internal stores).
Secretory products of pancreatic acinar cell

<table>
<thead>
<tr>
<th>Zymogens</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trypsinogen</td>
<td>Digestion</td>
</tr>
<tr>
<td>Chymotrypsinogen</td>
<td>Digestion</td>
</tr>
<tr>
<td>Proelastase</td>
<td>Digestion</td>
</tr>
<tr>
<td>Proprotease E</td>
<td>Digestion</td>
</tr>
<tr>
<td>Procarboxypeptidase A</td>
<td>Digestion</td>
</tr>
<tr>
<td>Procarboxypeptidase B</td>
<td>Digestion</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Active Enzymes</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>αAmylase</td>
<td>Digestion</td>
</tr>
<tr>
<td>Carboxyl ester lipase</td>
<td>Digestion</td>
</tr>
<tr>
<td>Lipase</td>
<td>Digestion</td>
</tr>
<tr>
<td>RNAase</td>
<td>Digestion</td>
</tr>
<tr>
<td>DNAase</td>
<td>Digestion</td>
</tr>
<tr>
<td>Colipase</td>
<td>Digestion</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Others</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trypsin inhibitor</td>
<td>Block of trypsin activity</td>
</tr>
<tr>
<td>Lithostathine</td>
<td>Constituent of protein plugs</td>
</tr>
<tr>
<td>Glycoprotein 2 (GP 2)</td>
<td>Formation of protein plugs</td>
</tr>
<tr>
<td>Pancreatitis-associated protein</td>
<td>Pancreatic growth, bacteriostasis</td>
</tr>
<tr>
<td>Na⁺, Cl⁻, H₂O</td>
<td>Hydration of secretions</td>
</tr>
<tr>
<td>Ca²⁺</td>
<td>Stone formation in pancreatitis</td>
</tr>
</tbody>
</table>
Pancreatic juice composition varies with secretory rate

Fig 43-7 p. 888
Pancreatic Secretion during Fasting and Feeding

![Graph showing trypsin output over time](Fig 43-8 p. 888)
## Phases of pancreatic secretion

<table>
<thead>
<tr>
<th>PHASE</th>
<th>STIMULANT</th>
<th>REGULATORY PATHWAY</th>
<th>% OF MAXIMUM ENZYME SECRETION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalic</td>
<td>Sight, Smell, Taste, Mastication</td>
<td>Vagal pathways</td>
<td>25</td>
</tr>
<tr>
<td>Gastric</td>
<td>Distention, Gastrin?</td>
<td>Vagal-cholinergic</td>
<td>10–20</td>
</tr>
<tr>
<td>Intestinal</td>
<td>Amino acids, Fatty acids, H⁻</td>
<td>CCK, Secretin, Enteropancreatic reflexes</td>
<td>50–80</td>
</tr>
</tbody>
</table>
Phases of pancreatic secretion

Fig 43-9 p. 891
Mechanisms protecting acinar cells from autodigestion

<table>
<thead>
<tr>
<th>PROTECTIVE FACTOR</th>
<th>MECHANISM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Packaging of many digestive proteins as zymogens</td>
<td>Precursor proteins lack enzymatic activity</td>
</tr>
<tr>
<td>Selective sorting of secretory proteins and storage in zymogen granules</td>
<td>Restricts the interaction of secretory proteins with other cellular compartments</td>
</tr>
<tr>
<td>Protease inhibitors in the zymogen granule</td>
<td>Block the action of prematurely activated enzymes</td>
</tr>
<tr>
<td>Condensation of secretory proteins at low pH</td>
<td>Limits the activity of active enzymes</td>
</tr>
<tr>
<td>Nondigestive proteases</td>
<td>Degrade active enzymes</td>
</tr>
</tbody>
</table>