Introduction to the endocrinology of the GI tract: neurogenic components, endocrine components and regulatory mechanisms. Enteroendocrine cells, hormone families, hormones of the GI tract and their neuroendocrine control.

- GI hormones: Gastrin / CCK family: gastrin, CCK; Secretin family: secretin, VIP, GIP, GLP; PP family: PPY, peptide YY, NPY; Other GI hormones: neurotensin, galanin, GRP, motilin, TRH, CGRH, SS, enkephalins, endorphins, SP.

- Neuroendocrine control of food intake

- Pathologies associated with GI hormones

Introduction

For each hormone, the student should know:

1. Its cell of origin
2. Its chemical nature, including:
   a. Distinctive features of its chemical composition
   b. Biosynthesis
   c. Whether it circulates free or bound to plasma proteins
   d. How it is degraded and removed from the body
3. Its principal physiological actions:
   a. At the whole body level
   b. At the tissue level
   c. At the cellular level
   d. At the molecular level
   e. Consequences of inadequate or excess secretion
4. What signals or perturbations in the internal or external environment evoke or suppress its secretion:
   a. How these signals are transmitted
   b. How that secretion is controlled
   c. What factors modulate the secretory response
   d. How rapidly the hormone acts
   e. How long it acts
   f. What factors modulate its action
Introduction

• The GI tract
• GI Hormones
• Pathologies

Overview of the GI tract: neurogenic and endocrine components, and regulatory mechanisms

Gastric glands, hormone secreting cells in the epithelial lining of the stomach and intestinal tract are present in deep invaginations of the mucosal surface scattered among cells of various functions. A. Schematic representation of an oxyntic pit. Note that the acid-producing parietal cells, the enzyme-producing chief cells, and the mucus-producing cells and the differentiating cells that renew the mucosal surface are all "open" to the lumen and come in direct contact with the luminal contents. The ECL (enterochromaffin like) cells, the somatostatin-secreting D cells, and the ghrelin producing cells are "closed" and have no direct contact with luminal contents. B. Schematic representation of the antral pit. Note that parietal cells are absent, and that the somatostatin producing D cells, the gastrin producing G cells, and the enterochromaffin cells are "open" and come in contact with the luminal contents. A similar arrangement of cells is seen in the crypts of the mucosa of the small and large intestines.
Introduction

• The GI tract

• GI Hormones

• Pathologies
Introduction

- The GI tract
- GI Hormones
- Pathologies

Overview of the GI tract: neurogenic and endocrine components, and regulatory mechanisms

Stimulus
Brush border
Exocytosis
Paracrine
Endocrine
Intrinsic reflex
Extrinsic reflex
Satiety

Overview of the GI tract: neurogenic and endocrine components, and regulatory mechanisms

• The GI tract
• GI Hormones
• Pathologies
Introduction

• The GI tract
• GI Hormones
• Pathologies

Overview of the GI tract: neurogenic and endocrine components, and regulatory mechanisms

extrinsic input / output
• intrinsic vs extrinsic
• inputs vs outputs
• neuronal vs endocrine
• vago - vagal reflexes
• endocrine reflexes
• Neuroendocrine reflexes

sensory receptors (mech / chem)
synapsis or neuro-musc-junction
intrinsic exocrine gland of GI syst

Overview of the GI tract: neurogenic and endocrine components, and regulatory mechanisms
Introduction

- The GI tract
- GI Hormones
- Pathologies

Enteroendocrine Cells

Overview of the GI tract: neurogenic and endocrine components, and regulatory mechanisms

Gastrointestinal Hormones

- The GI tract
- GI Hormones
- Pathologies

GI hormones are clustered into families having similar / overlapping functions
Gastrointestinal Hormones

- The GI tract
- GI Hormones
- Pathologies

GI hormones are clustered into families having similar / overlapping functions

examples of articles from Time magazine on the importance of GI hormones
Gastrin / CCK family

- **The GI tract**
  - Gastrin, stimulate gastric acid secretion. Its release from G antral cells (open cells) is induced by aromatic aa, small peptides, and Ca in the GI tract. SS release from neighboring D cells in response to acidification is a major inhibitor of gastrine.
  - CCK (5 aa), inhibits gastric emptying, pancreatic enzyme secretion, gallbladder emptying, induced satiation, and memory enhancement. Its release is induced by fat and proteins in the GI tract. GRP and Bombesin also stimulate CCK release. Stimulation of PKA and PKC pathways result in increase CCK mRNA.
  - The two CCK receptors (A in gut and B in brain) share 48% homology at the aa level.
  - The oxyntic gastrin receptor is identical to the CCK-B one and both are coupled to PLC.
  - Glucocorticoids transiently stimulate increases in CCK-A receptor mRNA stability without affecting transcription.

- **GI Hormones**
  - Gastrin, stimulate gastric acid secretion. Its release from G antral cells (open cells) is induced by aromatic aa, small peptides, and Ca in the GI tract. SS release from neighboring D cells in response to acidification is a major inhibitor of gastrine.
  - CCK (5 aa), inhibits gastric emptying, pancreatic enzyme secretion, gallbladder emptying, induced satiation, and memory enhancement. Its release is induced by fat and proteins in the GI tract. GRP and Bombesin also stimulate CCK release. Stimulation of PKA and PKC pathways result in increase CCK mRNA.
  - The two CCK receptors (A in gut and B in brain) share 48% homology at the aa level.
  - The oxyntic gastrin receptor is identical to the CCK-B one and both are coupled to PLC.
  - Glucocorticoids transiently stimulate increases in CCK-A receptor mRNA stability without affecting transcription.

- **Pathologies**

The gastrin / CCK family has a major role in gastric / duodenal interactions.
The gastrin / CCK family has a major role in gastric / duodenal interactions.
The gastrin / CCK family has a major role in gastric / duodenal interactions
The gastrin / CCK family has a major role in gastric / duodenal interactions.

Cellular actions of gastrin, acetylcholine, and histamine on the parietal cell. Convergence of signaling pathways results in synergistic stimulation of hydrochloride acid.
Gastrin / CCK family

- The GI tract
- GI Hormones
- Pathologies

Actions of gastrin and PACAP in ECL cells. Both gastrin and PACAP stimulate G-protein-coupled receptors to activate the IP3 (inositol trisphosphate)/DAG (diacylglycerol phosphate) pathway and increase intracellular Ca2+. IP3 stimulates release of Ca2+ from the endoplasmic reticulum (ER), and DAG-dependent activation of protein kinase C (PKC) results in phosphorylation and activation of membrane calcium channels. Increased Ca2+ triggers release of preformed histamine from storage granules and induces expression of histidine decarboxylase (HDC), the enzyme that catalyzes histamine formation, chromogranin (CGA) and vesicular monoamine transporter type 2 (VMAT-2).

Direct and indirect feedback regulation of gastrin secretion. Gastrin secretion is positively regulated by luminal nutrients and gastrin releasing peptide (GRP), and negatively regulated by somatostatin (SST). Gastrin reaches D cells in both the antral and duodenal mucosae by paracrine or endocrine pathways and stimulates them to secrete SST. Increased luminal H+ concentrations stimulate antral and duodenal D cells to secrete SST. Increased H+ concentrations in the duodenum and luminal nutrients in the intestine increase secretion of enteric hormones, which stimulate D cells in the gastric and duodenal mucosae to secrete SST. Increased luminal H+ concentrations are sensed by neuronal chemoreceptors and initiate vagal reflexes, which result in decreased release of GRP and decreased cholinergic inhibition of D cells.
The gastrin / CCK family has a major role in gastric / duodenal interactions.
Gastrin / CCK family

- The GI tract
- GI Hormones
- Pathologies

The gastrin / CCK family has a major role in gastric / duodenal interactions

The enterogastrone effect

- The gastrin / CCK family has a major role in gastric / duodenal interactions
Gastrin / CCK family

- The GI tract
  - GI Hormones
  - Pathologies

Effects of ingestion of a standardized liquid meal (arrow) on plasma cholecystokinin, gall bladder contraction, and pancreatic chymotrypsin secretion in normal subjects.

Actions of CCK on pancreatic secretion and bile flow. Major direct actions are indicated by solid blue arrows. Effects of questionable physiological significance are indicated by the dotted blue arrows.

Regulation of CCK secretion. Red arrows indicate inhibitory influences. LCRF = Luminal Cholecystokinin Releasing Factors.
Secretin / VIP family

- **The GI tract**
  - secretin, stimulate pancreatic bicarbonate / enzyme and hepatic bile secretion, and LES relaxation. Its release is induced by acid, bile, FA, and peptides GI
  - VIP, stimulates LES and gastric receptive relaxation, descending relaxation of intestine, water / electrolyte secretion from colon, biliary / pancreatic secretion, and promotes lipolysis. VIP gene expression is regulated by cAMP, PKC, and Ca. Outside the GI is modulated by E2, cortisol T3/T4, retinoic acid and IGF I
  - GIP, stimulates insulin and inhibits acid secretion. Its release is induced by Glu, Prot, aa, and FA in GI tract
  - GLP has insulinotropic effects and inhibits gastric motility. Its release is induced by Glu and aa in GI tract
  - the VIP / PACAP receptor has homology with secretin, GLP-1, PTH, GHRH, and calcitonin glycoprotein receptors
  - VIP-I receptor is found in gut and VIP-2 receptor in brain. VIP, cAMP, IP3, PKC, Ca
  - VIP and NO colocalize in the myenteric plexus of the gut. Both are inhibitory in GI tract
  - secretin receptor couples to stimulation of AC, Ca, & PLC

- **GI Hormones**

- **Pathologies**

The secretin / VIP family also has a major role in gastric / duodenal interactions
Secretin / VIP family

- The GI tract
- GI Hormones
- Pathologies

The secretin / VIP family include secretin, the VIP, GIP and GLP hormones

The secretin/glucagon family of peptides. Amino acids are represented by the single letter amino acid code. Residues colored red are identical with those in corresponding positions in secretin. Residues colored cyan or green are identical with those in corresponding positions in at least three family members. Beyond residue 30, in the C-terminal region, sequence divergence is extensive. Residues colored red are identical with those in corresponding positions in secretin. Residues colored cyan or green are identical with those in corresponding positions in at least three family members. Beyond residue 30, in the C-terminal region, sequence divergence is extensive. Residues colored red are identical with those in corresponding positions in secretin. Residues colored cyan or green are identical with those in corresponding positions in at least three family members. Beyond residue 30, in the C-terminal region, sequence divergence is extensive. A = alanine, C = cysteine, D = aspartic acid, E = glutamic acid, F = phenylalanine, G = glycine, H = histidine, I = isoleucine, K = lysine, L = leucine, M = methionine, N = asparagine, P = proline, Q = glutamine, R = arginine, S = serine, T = threonine, V = valine, W = tryptophan, Y = tyrosine.

The secretin / VIP family also has a major role in gastric / duodenal interactions.
The secretin / VIP family include secretin, the VIP, GIP and GLP hormones.

Actions of secretin on bicarbonate secretion by pancreatic and bile duct epithelial cells. Stars indicate processes that are stimulated by secretin through increased cyclic AMP formation and protein kinase A-dependent phosphorylation.

Synergistic effects of secretin and CCK on bicarbonate secretion. Secretin alone, CCK alone or secretin and CCK in combination were infused intravenously in six normal human subjects. Bicarbonate output was assessed in samples of duodenal fluids collected through a naso-gastric tube.
Secretin / VIP family

- The GI tract

- GI Hormones

- Pathologies

Schematic representation of the actions of secretin and feedback regulation of its secretion. Solid arrows indicate stimulation; dashed arrows indicate inhibition. LSRF = luminal secretin releasing factors.

The secretin / VIP family include secretin, the VIP, GIP and GLP hormones

Secretin / VIP family

- The GI tract

- GI Hormones

- Pathologies

How GLP-1 might work?

The secretin / VIP family include secretin, the VIP, GIP and GLP hormones
The secretin / VIP family include secretin, the VIP, GIP and GLP hormones

How GLP-1 might work?

The incretin effect. Infusion of a solution of 500 mg of glucose intrajejunally produces a smaller increase in plasma glucose concentration than infusion of the same amount of glucose intravenously (upper panel), but the jejunal infusion elicits a much greater increase (55-fold vs. 12-fold) in insulin secretion.

Effects of different dietary nutrients in secretion of incretin hormones. Eight healthy volunteers were fed 375-calorie meals consisting of only glucose, protein, or fat. Venous blood was sampled at the indicated times. A. Glucose and to a probably increased plasma concentrations of GIP (glucose-dependent insulinotropic peptide). B. Glucose and protein promptly increased plasma levels of GLP-1 (glucagon-like peptide 1), but the response to the fatty meal was delayed. Note the difference in the scales for plasma concentrations of GIP and GLP in panels A and B, and note also that peak plasma concentrations of both hormones were achieved in 30 minutes after the glucose meal. C. Plasma concentrations of insulin were increased only after the glucose meal, and peak plasma insulin concentrations were unchanged after ingesting protein or fat, despite increased secretion of GIP and GLP-1, illustrating the glucose dependence of the incretin effect.
The GI tract

GI Hormones

Leptin and food intake

Pathologies

Secretin / VIP family

How GLP-1 might work?

Post-translational processing of proglucagon. Black arrows indicate dibasic sites of cleavage by hormone convertases. The green arrow points to a monobasic cleavage site. The cross-hatched area represents the hexapeptide fragment now present in the mature form GLP-1. The final products of pancreatic alpha cells and intestinal L cells are determined by the presence of different convertases in the two cell types. GRPP = Glicentin-related pancreatic peptide; GLP-2 = glucagon-like peptide-2.

Effects of glucagon-like peptide-1 (GLP-1) infusion on gastric emptying and acid secretion following ingestion of a standardized liquid meal in nine healthy male volunteers. Subjects were given a constant infusion of either saline or 1.2 pmol of GLP-1/kg/minute beginning 30 minutes before eating and continuing through the subsequent 4 hours (green bar). The arrow indicates the time of meal ingestion.

The ileal brake. (GLP-1 = glucagon-like peptide-1)
The PP family include PPY, peptide YY and NPY, others include neurotensin, galanin, GRP, motilin, TRH, CGRH, SS, enk, end, SP

The PP family and others

- **Gi Hormones**
  - PPY, inhibits pancreatic excretion. Its release is induced by fat in the GI tract.
  - PYY, inhibits acid and pepsin secretion from stomach, water and chloride from jejunum, slows small intestine transit time, inhibits pancreatic exocrine secretion and colonic motor activity. Its release is induced by Prot, FA bile acids and a in GI tract.
  - NPY, inhibits gastric and small intestinal motility and secretion. Centrally is a potent enhancer of food intake. It acts through a 7 transmembrane receptor negatively coupled to AC and is associated to Ca mobilization.
  - At least 5 receptor types (Y1, Y2, Y3, Y4, Y5) have been reported.
  - Neurotensin, inhibits gastric / pancreatic secretion, and stimulates colonic motility. Its release is induced by fat.
  - Galanin, inhibits gastric emptying, slows colonic transit time, and increases food intake in the CNS through a G-protein. Its release is induced by intestinal distention.
  - GRP, stimulates gastric release from antrum, contracts LES. Its release is induced by cholinergic stimulation.
  - Motilin, regulates motor complexes, contracts gall bladder, relaxes pylorus. Its release is induced by acidification of duodenum and gastric contraction.
  - TRH, release by pancreas / stomach, inhibits gastric acid, amylase, lipase, mucosal cholesterol synthesis.
  - CGRH, induced vasodilation in response to glucose.
  - SS, inhibits peptide hormone, fluid / electrolyte secretion.

- **Pathologies**

The PP family and others
Amino acid sequences of the PPY (PPfold) family of peptides using the single letter amino acid code. Residues shown in red are identical in corresponding positions in all three peptides. Residues shown in cyan or green are identical with those in corresponding positions in two family members. A = alanine, C = cysteine, D = aspartic acid, E = glutamic acid, F = phenylalanine, G = glycine, H = histidine, I = isoleucine, K = lysine, L = leucine, M = methionine, N = asparagine, P = proline, Q = glutamine, R = arginine, S = serine, T = threonine, V = valine, W = tryptophan, Y = tyrosine.

Others neuropeptides include neurotensin, ghrelin, galanin, GRP, motilin, TRH, CGRH, SS, enk, end, SP.
The motilin-ghrelin family.

A. Post-translational processing of prepromotilin and preproghrelin. Cleavage of preproghrelin releases ghrelin from the N terminus and a second peptide called obestatin, which may have biological activity.

B. Amino acid sequences of motilin and ghrelin represented with the single amino acid code. Insertion of a gap between residues 15 and 16 in motilin optimizes the correspondence to the sequence of ghrelin and probably represents the loss of a codon. The octanoate held in ester linkage with the serine at position 3 of ghrelin is essential for activity.

Effects of motilin on gastric muscle tone. An intragastric balloon was placed in the stomachs of normal fasted volunteers and filled with air. Changes in gastric muscle tone were detected as changes in balloon volume; increased muscle tone decreases balloon volume. Infusion of atropine, which blocks acetylcholine receptors, resulted in expansion of the balloon, indicating a decrease in tone. Infusion of motilin alone (not shown) or during the continued infusion of atropine increased gastric tone as indicated by decreases in volume of the balloon, effects mediated by parasympathetic stimulation of gastric muscle.
GI Endocrine Pathophysiology

- The GI tract
- GI Hormones
- Pathologies

Some endocrine pathologies involved in disfunction of the GI system
GI Endocrine Pathophysiology

• The GI tract
• GI Hormones

• Pathologies

Some endocrine pathologies involved in disfunction of the GI system