Introduction to Gastrointestinal Physiology and GI Hormones
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OBJECTIVES:

1. Describe the general organization of the gut.
2. Identify the levels of neural control and describe the interaction between these components.
3. Compare and contrast the neural, hormonal, and paracrine control mechanisms.
4. List the stimuli for the release of the main hormones.
5. Differentiate the physiological and pharmacological actions of the main gut hormones.

Suggested Reading: Berne & Levy pp. 539-543, 545-548

I. FUNCTION OF THE GI TRACT

The main function is the conversion of ingested material to a form that is easily absorbed by cells that line the gut (enterocytes). Optimal conditions for this require regulation of the movements of smooth muscle (Motility); addition of digestive enzymes, fluids, and electrolytes to the lumen to insure proper dilution and regulation of pH (Secretion); and movement of digested end products across the cell membrane for delivery to the rest of the body (Absorption). Undigested residual material is excreted as feces. The process requires coordination of many cells/tissues; this coordination is accomplished by the activity of nerves, hormones, paracrine agents and autocrine agents.

II. FUNCTIONAL ANATOMY

A. Basic structure (fig 1):

A long muscular tube with several functional segments.

1. Mouth: chewing, saliva added, formation of bolus, initiate digestion
2. Esophagus: conduit
3. Stomach: major function is storage.

   a. Other functions include physical grinding of solids, acidification, some digestion, regulation of flow into intestine.
   b. Formation of chyme, the term for a mixture of food particles, enzymes, and gut secretions.

4. Small Intestine: three division- duodenum, jejunum, ileum
a. main function is digestion and absorption

5. Large Intestine: three division: cecum, colon, rectum
   a. main functions include drying of chyme into feces, storage of feces, final absorption of water and electrolyte.

B. Sphincters: (figure 2)
   Between each major region, there is a thickening of the muscle (circular) layer called a sphincter. These function to regulate flow.
   1. Upper & Lower Esophageal
   2. Pyloric
   3. Oddi
   4. Ileo-cecal
   5. Anal (internal & external)

Figure 1. Summary of Functions
Figure 2. Sphincters

C. Associated structures
These serve to facilitate digestion and absorption by adding fluid, electrolyte, and digestive enzymes and co-factors.

1. Salivary glands
2. Liver
3. Gallbladder
4. Pancreas

D. Organization of the gut wall (Figure 3)
From outside to inside there are multiple concentric layers

- Serosa
- Longitudinal muscle
- Myenteric Plexus
- Circular muscle
- Submucosal plexus
- Submucosa
- Muscularis mucosa
- Mucosa (epithelium & lamina propria)
III. MECHANISM OF CONTROL

A. A large number of regulatory cells and mechanisms are needed to organize and control the functions of the gut.

1. There are $10^8$ neuronal cell bodies in the gut.
2. There are $>20$ identified hormones.
3. 70 to 80% of all of the body's immune cells are found in the gut (GALT or Gut Associated Lymphatic Tissue).
4. Note that even with all these cells, there are still 10 non-mammalian cells for every mammalian cell. Most of these non-mammalian cells are bacteria ($>500$ species in colon alone).

B. Neural: Fine control of discrete regions. Mediated by both extrinsic (cell bodies outside of the gut) and intrinsic (cell bodies within the wall of the gut) nervous systems. The latter is referred to as the Enteric Nervous System (ENS).
C. Hormonal/Endocrine Control is more generalized. The **Hormone** is released into blood which then carries it to distant target site where it acts on cells expressing the appropriate receptors. The gut is largest endocrine organ in body.

D. **Paracrine agent**: These are released into extracellular space, diffuse short distances to act on adjacent cells with appropriate receptors. Paracrine cells often have a cytoplasmic projection so as to release paracrine agents over long distances.

E. **Autocrine agent**: These are released into the extracellular space and act on cells of its origin. This is an important mode of action for growth factors.

![Three Mechanisms of Communication Mediate Responses in the GI Tract](image)

Figure 4.

IV. **NEURAL CONTROL OF THE GUT**

A. The **Extrinsic nervous system** is part of the **autonomic nervous system** and shares many of its general characteristics. (Figure 5)
1. **Parasympathetic nervous system** (Figure 6)

   a. **Preganglionic fibers** to the esophagus through the transverse colon originate in nuclei of the brain stem (**Dorsal Motor Nucleus of the Vagus (DMV)**) and travel in the **vagus nerve** (**Xth cranial nerve**). Preganglionic fibers to the remainder of the colon, rectum, and anus originate in the sacral division of the spinal cord (**S2-4**) and travel in the **pelvic nerve**.

   b. Preganglionic neurotransmitter is **acetylcholine**.

   c. **Postganglionic cell bodies** are in the ganglia of the enteric nervous system.

   d. Postganglionic transmitter may be acetylcholine or one of many neurotransmitters released by neurons of the enteric nervous system (see B below).

   e. Generally parasympathetic stimulation leads to an overall excitation of the gut (e.g. increased motility, increased secretion).

   f. Vagus nerve contains many axons. There are about 90% afferent fibers and 10% efferent. These relatively few efferent fibers (about 5000) innervate many (**10^8**) enteric neurons, therefore parasympathetic activation of gut leads to widespread activation of the gut via the enteric nervous system.
2. **Sympathetic nervous system** (Figure 6)

   a. **Preganglionic fibers** originate in the thoracic and lumbar portions of the spinal cord and pass through the sympathetic paravertebral (chain) ganglia to synapse with postganglionic neuronal cell bodies located in the prevertebral ganglia (celiac ganglia, superior and inferior mesenteric ganglia). The preganglionic transmitter is acetylcholine.
   
   b. Postganglionic fibers originate in prevertebral ganglia. Neurotransmitter is primarily norepinephrine.
   
   c. Most postganglionic fibers terminate on other neurons in the enteric nervous system. Stimulation of sympathetic fibers usually results in a general inhibition of gut function (e.g. decreased motility) as a result of an inhibition of neural activity within the enteric nervous system. This is mainly the result of presynaptic inhibition of acetylcholine release from enteric neurons. This inhibition is mediated by activation of alpha-2 receptors on presynaptic terminal of the cholinergic neuron.
   
   d. Some fibers terminate on blood vessels where they cause vasoconstriction, some terminate on glands where they cause secretion and some terminate on smooth muscle cells of
sphincters where they cause contraction. This contractile effect on sphincteric smooth muscle is opposite to the general inhibitory effect of sympathetic stimulation of gut motility. Both, however, prevent movement of chyme through the gut. (Figure 7)

3. Afferent Nerves (Figure 8).

a. Afferent nerves detect sensory information from various layers of the gut (mucosa, muscle and serosa). There are 3 types.

1. **Vagal afferent fibers** which originate in the nodose ganglion and connect the gut to the **Vagal Complex** (Nucleus of the Tractus Solitarius (NTS) and Dorsal Motor Nucleus (DMN)) in the brain stem.

2. **Extrinsic Primary afferent neurons** which originate in **Dorsal Root Ganglion** and connect the gut to the prevertebral ganglion and spinal cord.

3. **Intrinsic Primary afferent neurons (IPANs)** which originate in the myenteric and submucosal neural plexuses of the enteric nervous system.
4. Long Arc Reflexes

a. Both the parasympathetic and sympathetic nervous system participate in reflex arcs that coordinate activity over long distances and between different regions of the gut. These are termed **Long Arc Reflexes**. In these reflexes, both the afferent and efferent neurons are extrinsic to the gut although their effect is mediated through the enteric (intrinsic) nervous system.

b. Long arc reflexes using the parasympathetic nervous system are generally excitatory **VagoVagal Reflexes** (both afferent and efferent neurons are in the vagus nerve. (Figure 9). The vagal efferent ends on neurons of the enteric nervous system.
c. Long arc reflexes using the sympathetic nervous system are generally inhibitory. The afferent component is usually an extrinsic primary afferent neuron and the efferent neuron is a sympathetic neuron arising in the intermediate lateral horn of the thoracic-lumbar spinal cord and in the **prevertebral ganglion**. The efferents end on neurons of the enteric nervous system. The prevertebral ganglia neurons receive input from passing primary afferent neurons and from **viscerofugal** or **intestinofugal neurons** arising in the enteric nervous system (Figure 10). These mediate reflexes through the prevertebral ganglia and modify sympathetic efferent neurons. Sympathetic reflexes can pass through the spinal cord and can also pass between sympathetic prevertebral ganglia. An example is the **Intestino-Intestinal Reflex** which mediates inhibition between regions of the intestine (Figure 11).
**B. Enteric Nervous System (ENS) or Intrinsic Nervous System**

1. **General Comments**
   
a. Neuronal cell bodies and fibers are contained within the wall of the gut. The number of neurons in ENS is about equal to the number in the spinal cord ($10^8$).
   
b. Often called the **Mini-brain**.
   
c. ENS is comprised of two ganglionated plexuses and interconnecting fibers: the **myenteric plexus** and **submucosal plexus** (Figure 12).
d. ENS controls local function via reflexes that operate independently of the central nervous system. These are called **Short arc reflexes** because they control local activity and do not extend more than a few cm from the stimulus. **Afferent** and **Efferent** neurons are wholly within the enteric nervous system. The **Peristaltic Reflex** is an example. These reflexes can be modified by extrinsic nervous system. (Figure 13.)
e. ENS neurons act as postganglionic neurons of the parasympathetic nervous system and as the end organ of sympathetic nervous system.

f. ENS integrates inputs from afferent nerves, sympathetic and parasympathetic nerves, and nerves in the enteric nervous system (mini-brain). Most all information enters ENS system for processing and determination of final response of gut tissues.

g. Sensory or afferent neurons for local arc reflexes are contained in the enteric nervous system and are called Intrinsich Primary Afferent Neurons or IPANs (see figure 8).

h. There are also enteric neurons that project axons to the prevertebral ganglia (intestinofugal or viscerofugal neurons). These are involved in long arc reflexes and in regulating sympathetic input to the enteric neurons.

i. A variety of neurotransmitters are found in enteric neurons. Most neurons contain and release more than one neurotransmitter. Examples include:

   i. **Acetylcholine (ACh):** The main transmitter in the enteric nervous system. Ach stimulates both increased smooth muscle contraction and secretions from cells and glands. Found in excitatory motor neurons and interneurons.

   ii. **Enkephalins (opioid peptides):** Generally inhibitory and restrain release of ACh from enteric neurons. Found mainly in interneurons.

   iii. **Tachykinins (TK) (substance P and neurokinin A):** major contractile transmitter mediating non-cholinergic responses. Found in excitatory motor neurons and interneurons.

   iv. **Vasoactive intestinal peptide (VIP):** Major relaxant transmitter for smooth muscle and excitatory transmitter for secretory cells. Found in inhibitory motor neurons and excitatory secretomotor neurons.

   v. **Gastrin releasing peptide (GRP):** Found in long interneurons of the intestine and in gastric enteric neurons that stimulate acid secretion and gastrin secretion.

   vi. **Somatostatin:** Major inhibitory transmitter of the gut. Found in interneurons where it regulates the release of other neurotransmitters.

   vii. **Nitric Oxide:** relaxant transmitter; A gaseous transmitter made on demand from L-Arginine by Nitric Oxide Synthase (NOS).

j. Many other neurotransmitters are contained in enteric neurons.

k. Most tachykinin neurons also contain acetylcholine and account for 40-50% of all ENS neurons. All VIP neurons contain NOS and
account for 20-30% of all ENS neurons. There is no overlap between TK/ACh neurons and VIP/NOS neurons.

1. **Myenteric Plexus**
   
a. This plexus is located in the muscularis externa between the longitudinal and circular muscle layers. (Figure 9).
b. Fibers project mainly into the underlying muscle layer, but also into submucosal plexus and mucosa. Activity primarily responsible for control of muscle activity.

2. **Submucosal Plexus**
   
a. Located in submucosa.
b. Fibers project into underlying submucosa and mucosa (including muscularis mucosa), but also to myenteric plexus. In humans and large animals, these neurons also project to the innermost layers of circular muscle.
c. Primarily responsible for control of secretion

### V. **HORMONAL CONTROL OF THE GUT**

A. **General comments**

1. The gut is largest endocrine organ in the body.
2. Hormones are released from **enteroendocrine cells** located in mucosa of gut. These cells extend from the lumen to basement membrane. The **Lumenal (apical) membrane** has receptors for chemical components of chyme and, if conditions are appropriate, the cell releases hormone into blood from the basal side (see Figure 4).
3. The hormone is distributed throughout the body by the circulation and cells which contain appropriate receptors for the hormone respond.
4. Hormonal mechanisms are relatively more important in stomach and small intestine and associated structures than in esophagus and colon.
5. All gut hormones are **polypeptides** and all are amidated on the C-terminal end.
6. To be accepted as a hormone, candidate must be shown to be present in the gut, synthesized by an endocrine cell in the gut, the structure identified, released by an appropriate physiological stimulus, produce an appropriate physiological effect when infused exogenously at the appropriate blood level, and to be blocked by appropriate antagonists or antisera.
There are many candidates which have met many but not all of these
criteria. Hormones which have met all criteria include gastrin,
cholecystokinin, secretin, glucose-dependent insulinotrophic
peptide (GIP). Stimuli for release and important physiological
actions are listed in Tables 1 and 2.

<table>
<thead>
<tr>
<th>Table 1. Releasers of Gastrointestinal Hormones</th>
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<tbody>
<tr>
<td>Protein</td>
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<tr>
<td>Fat</td>
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<tr>
<td>Carbohydrate</td>
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<td>Acid</td>
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<td>Distension</td>
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<tr>
<td>Vagal Stimulation</td>
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<td>S=stimulation; S- = of secondary importance; I=inhibition; N=no effect.</td>
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<table>
<thead>
<tr>
<th>Table 2. Important PHYSIOLOGICAL Actions of Gastrointestinal Hormones</th>
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<tbody>
<tr>
<td>Action</td>
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<tr>
<td>Acid Secretion</td>
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<tr>
<td>Pancreatic HCO3 Secretion</td>
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<tr>
<td>Pancreatic Enzyme Secretion</td>
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<tr>
<td>Bile HCO3 Secretion</td>
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<td>Gallbladder Contraction</td>
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<tr>
<td>Gastric Emptying</td>
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<tr>
<td>Insulin Release</td>
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<tr>
<td>Mucosal Growth</td>
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<tr>
<td>Pancreatic Growth</td>
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**B. Gastrin**

1. Exists in several molecular sizes: main form is G-17, but also exists as
   G-14, G-34 and larger forms.
2. C-terminal end is active as a fragment but has only 1/6 the potency of
   G17.
3. Exists in sulfated and nonsulfated forms.
4. Found in G cells located in gastric antrum.
5. Released by:
   a. mechanical distension of antrum,
   b. vagal stimulation,
c. presence of amino acid/peptides in antrum.

6. Release is inhibited when the antral pH drops below pH of 2 (a feedback loop involving somatostatin mediates this effect).

7. Main physiological actions:
   a. stimulate acid secretion,
   b. stimulate growth of gastric mucosa.

C. Cholecystokinin (CCK)

1. Main form is CCK-33, but also exists as CCK-58 and CCK-5 (may be neural form).
   A fragment of the C-terminal end is active but is much less potent than CCK-33.
2. Exists in only the sulfated form.
3. Located in I cells of the upper small intestine.
4. Released by amino acids/peptides and by monoglycerides/fatty acids in upper small intestine.
5. Main physiological actions:
   a. stimulates enzyme secretion by pancreas,
   b. stimulates pancreatic growth,
   c. stimulates gallbladder contraction,
   d. inhibits gastric emptying.

Gastrin and Cholecystokinin make up a family of hormones. The C-terminal end (last 5 amino acids Gly-Trp-Met-Asp-Phe) is identical in these hormones. This C-terminal end is also responsible for receptor binding. This means that at high concentrations, CCK and Gastrin can bind to each others cognate receptor and produce the same effects, albeit with lower potency and efficacy. Sulfation of gastrin is required for it to bind to the CCK receptor and mimic CCK.

At pharmacological levels or in pathological (tumor) conditions (see Table 3), CCK and Gastrin can interact with each others receptors, but they are weaker stimulants. If the weaker agent prevents the more potent agent from binding the receptor, there is a net lower level of stimulation. This property is called: competitive antagonism. It is the N-terminal end of the full molecule that makes each more potent at its own receptor.

D. Secretin

1. Only one molecular form: 27 AA. The whole sequence is needed for activity (no active fragment).
2. Located in S cells in upper small intestine.
3. **Released** mainly by presence of acid (i.e. low pH) and to a lesser extent monoglyceride/fatty acid in duodenum.

4. Main **physiological actions**:
   a. stimulates secretion of bicarbonate from duodenal glands, pancreas and biliary system,
   b. stimulates pancreatic growth,
   c. inhibits acid secretion.
   d. inhibits gastric emptying

E. **Glucose-dependent Insulinotropic Peptide (GIP)**

1. Only one molecular form: 42 AA. The whole sequence is needed for activity.
2. Located in K cells of upper small intestine.
3. **Released** by presence of monoglyceride/fatty acid, amino acid/peptides, or carbohydrates in duodenum.
4. Main **physiological actions**:
   a. stimulates insulin secretion by the pancreas
   b. inhibits acid secretion by parietal cells of stomach.

Secretin and GIP are components of the **Secretin Family** which also includes Glucagon, Vasoactive Intestinal Peptide (VIP), and Peptide Histidine Isoleucine (PHI). The latter two are neurotransmitters. In this family, there is sequence homology throughout structure, but no active fragment; the whole sequence is needed for activity. Competitive antagonism occurs between members of this family.

<table>
<thead>
<tr>
<th>TABLE 3: Pharmacological Actions (Actions at supraphysiological serum levels)</th>
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<tbody>
<tr>
<td><strong>Action</strong></td>
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<tr>
<td>Acil Secretion</td>
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F. Other Important Candidate Hormones
   1. **Enteroglucagon**: released from intestinal enteroendocrine cells in response to a decrease in blood glucose; causes liver to increase glycogenolysis and gluconeogenesis as well as increase lipolysis.
   2. **Pancreatic Polypeptide Family: Pancreatic polypeptide (PP)** released from pancreas in response to meal (especially amino acids) and **Peptide YY (PYY)** released from ileum in response to lipids. Also released by neural stimulation or by other hormones. Physiological effect is inhibition of pancreatic enzyme secretion and an indirect relaxation of gallbladder. PYY may play a role in feeding behavior/satiety. A third member of family found in enteric nerves is called **neuropeptide Y (NPY)**. Since this is a family of related peptides, they can all mimic each other’s actions at high concentrations.
   3. **Somatostatin**: released from intestinal cells in response to meal and acid as well as by neural and hormonal factors. Inhibits secretion, motility and hormone release throughout gut. Also found in nerves of gut and brain, in endocrine cells of pituitary, and paracrine cells of the gastric mucosa & pancreas.
   4. **Motilin**: released from intestine by neural stimulation and maybe by presence of biliary fluid in duodenum. Causes increased motility and may have a role in induction of migrating myoelectric complex (MMC) in stomach and upper intestine. A recently identified relative, **ghrelin**, may play a role in feeding/satiety behaviors. Motilide antibiotics act on motilin receptors to increase motility and are under consideration as agents with which to treat decreased intestinal and colonic transit.
   5. Many other candidate hormones are presently being studied however physiological characteristics for these have yet to be identified.

VI. **PARACRINE CONTROL OF THE GUT**

   A. Release of paracine peptide into extracellular space where it diffuses to adjacent or nearby cells. Those cells with appropriate receptors are excited or inhibited.
   B. Release of **somatostatin** by antral D cells diffuses to nearby antral G cells where it inhibits the release of gastrin by the G cell. (Note: somatostatin can thus be a neurotransmitter, hormone and a paracrine agent).

VII. **STUDY QUESTIONS**

   1. Short Arc reflexes
A. involve the parasympathetic nerves.
B. usually only regulate a few cm of activity.
C. control mainly gastric secretion.
D. do not involve the submucosal plexus.
E. are mediated by the paravertebral ganglia.

2. Gastrin

A. Is release by cells of the duodenum.
B. Is a member of the secretin family of hormones.
C. Is present in nerves and endocrine cells.
D. Is released by vagal nerve stimulation.
E. Is released into the gastric lumen.

3. At physiological concentrations, secretin

A. Stimulates gastric emptying.
B. Inhibits acid secretion.
C. Causes VIP release.
D. Causes gallbladder contraction.
E. Simulates salivary secretion.

4. Most gut hormones are

A. Secreted from nerve terminals
B. Released in response to components of the chyme.
C. Complex carbohydrate molecules.
D. Located in cells of the stomach.
E. Present in the serosal layer of the gut.

5. Sympathetic nerves to the gut

A. Mainly synapse on enteric neurons.
B. Usually cause smooth muscle contraction.
C. Are rare in the intestine.
D. Release acetylcholine as neurotransmitter.
E. Originate in the brain stem.

VIII. Answers: 1 = B; 2 = D; 3 = B, 4=B, 5=A