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M1 - GI Sequence

Nerves and Hormones

John Williams, M.D., Ph.D.

Winter, 2009
OVERVIEW OF GASTROINTESTINAL TRACT

Gastrointestinal System

1. Salivary glands
2. Esophagus
3. Stomach
4. Small Intestine
5. Colon
6. Rectum
7. Pancreas
8. Liver
9. Gallbladder

BASIC PROCESSES OF THE GI TRACT

General Functions of Gastrointestinal Motility

1. Segmental contractions leading to nonpropulsive mixing and churning.
2. Propulsive movements including peristalsis moving food and digestive products caudal.
3. Reservoir function of some hollow organs made possible by sphincters at outlet.
DIGESTION

The chemical breakdown of food into molecules able to cross the mucosa (absorption) and gain entry to the blood.

Overall Fluid Balance of the GI Tract

Ingestion 2 liters/day

Absorption 8.8 liters/day

Secretion 7 liters/day

Feces 0.2 liter/day

Phases of GI Regulation

Origin of Stimuli

cephalic phase

gastric phase

intestinal phase

Cephalic Stimuli
taste, smell, sight, emotions

Gastric and Intestinal Luminal Stimuli
mechanoreceptors - volume, pressure
chemoreceptors - amino acids, fatty acids, pH
osmoreceptors - osmolarity

The digestive system received a large fraction of cardiac output, i.e., 25-30% at rest. Following a meal this blood flow increases. The three major arteries supplying blood to the GI tract are the celiac, superior mesenteric and inferior mesenteric. The venous drainage empties into the portal vein and perfuses the liver such that the liver is exposed to all absorbed molecules. The microcirculation of the GI tract is abundant and of high permeability ensuring adequate exchange. Most of the capillaries are of the fenestrated type. Lymphatic vessels are especially abundant in the small intestine and convey about a liter per day of lymph to the thoracic duct. The lymphatic system is the main route by which absorbed lipids reach the circulation.

The enteric nervous system, sometimes known as the “little brain” contains a similar number of neurons as the spinal cord and can function independent of the CNS. Morphologically its main components are the myenteric and submucosal plexus. It contains sensory or afferent neurons, interneurons, and motor or efferent neurons located within the bowel wall. Enteric neurons are organized into “hardwired” circuits that involve integration but can be modulated by the central nervous system through the autonomic nervous system, especially the Vagus nerve.

**Vagovagal or long reflex**: information from receptors in the smooth muscle or mucosa is relayed through the enteric nervous system to higher centers via vagal afferents. This may trigger a response carried by vagal efferents resulting in alteration of motility, secretion, or hormone release.
NEUROTRANSMITTERS INVOLVED IN GI REGULATION

NON-PEPTIDES
Acetylcholine
Norepinephrine
Serotonin
Nitric Oxide
Dopamine
Purinergic
(adenosine, ATP)

PEPTIDES
Substance P
CCK
Somatostatin
VIP
Enkephalin

Extrinsic parasympathetic and sympathetic innervation of the digestive system

Solid lines represent preganglionic and broken lines represent post-ganglionic fibers

Fig. 1-6 Granger, D, et al. Clinical Gastrointestinal Physiology. W.B. Saunders, Philadelphia, PA; 1985: 12.
The Vagus Nerve

The Vagus provides the primary neural control of the GI tract. It contains afferent fibers with cell bodies in the Nodose ganglion which project to the Nucleus Tractus Solitarius of the brain stem. Vagal efferents have their cell bodies in the Dorsal Motor Nucleus of the Vagus (DMV) in the adjacent brain stem. These motor fibers are small in number but powerful in effect and innervate the bulk of the gut as shown on Pages 15 and 17 as well as the heart and lungs. Visceral nocioceptive fibers (sensitive to stretch and chemical irritants) travel in sympathetic nerves and enter the spinal cord where it is projected to the brainstem and viserotopically mapped but poorly localized, often resulting in referred pain.
GENERAL PROCESSES AFFECTED BY GI REGULATORY MOLECULES

1. GI Secretion (stomach, pancreas, intestine)
2. GI Motility (stomach, intestine, gallbladder)
3. Endocrine Secretion (pancreatic islets)
4. Growth of GI Organs
5. Food Intake

“Incretin” – A hormone from the gut which is released in response to food and brings about secretion of insulin.
Gastrin-CCK Family

**GASTRIN**

Major Physiological Effects:
1. Gastric Acid Secretion
2. Gastric Mucosal Growth

G-4 minimal active fragment shared with CCK
G-5 Pentagastrin (synthetic)
G-17 “little” gastrin → Exist as both non-sulfated
G-34 “big” gastrin → and sulfated forms

**CHOLECYSTOKININ (CCK)**

Major Physiological Effects:
1. Gallbladder Contraction
2. Pancreatic Enzyme Secretion
3. Inhibition of Gastric Emptying

CCK-8
CCK-33 → All contain sulfated tyrosine
CCK-58

Both Gastrin and CCK are synthesized as larger precursors and post-translationally cleaved and processed resulting in multiple forms of the indicated number of amino acids with a common amidated carboxyl terminal. Gastrin is synthesized in G cells of stomach and released in response to protein and peptide in the stomach or neural stimulation through GRP. CCK is synthesized in I cells of the duodenum and jejunum and released in response to protein and fat in the intestine. G cell tumors (gastrinomas) are most common in pancreatic islets and led to extreme gastric acidity (Zollinger-Ellison Syndrome).

Secretin-GIP-VIP-Glucagon Family

**SECRETIN**

Major Physiological Effects:
1. Stimulation of bile and Pancreatic HCO₃ Secretion
2. Inhibition of Gastric Acid Secretion

Secretin is a 27 amino acid peptide synthesized by S cells in the duodenal/mucosa and released in response to acid (pH 4.5) in the duodenal lumen.

**GASTRIC INHIBITORY PEPTIDE (GIP)**

Major Physiological Effects:
1. Stimulation of Insulin Secretion
2. Inhibition of Gastric Acid Secretion

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**GLUCAGON**

Found in both pancreas and gut but processed in islets to glucagon and in gut to GLP-1 and GLP-2

**VASOACTIVE INTESTINAL PEPTIDE (VIP)**

Widely distributed neuropeptide most often inhibitory to muscle but stimulates glandular secretion.

Tumors (VIPomas) result in secretory diarrhea
Other GI Regulatory Molecules

Histamine - major stimulant of gastric acid secretion

Bombesin or GRP (Gastrin Releasing Peptide)
- stimulates Gastrin Release

Motilin - intestinal GI hormone
- regulates intestinal motility (MMC)

Enkephalins - neurocrine regulators
- of motility and secretion

Substance P – neuropeptide; usually excitatory

Somatostatin - universal inhibitory paracrine
- or endocrine regulatory peptide

GLP-1 - glucagon-like peptide 1
- formed by posttranslational processing
  of proglucagon in intestine.
  An important regulator of insulin secretion
  and appetite

GLP-2 - glucagon-like peptide 2 stimulates growth of
- intestinal mucosa

Inflammatory Mediators - Serotonin, cytokines,
- chemokines

Growth and Trophic Factors
- Insulin, TGF α, IGF

Ghrelin – an orexigenic (appetite stimulating) peptide
- present in the gastric mucosa whose release
  is inhibited by nutrients

The nomenclature for the cell of origin for each
molecule is listed above the bar.
Slide 4 – (Left) John Williams
Slide 4 – (Right) John Williams
Slide 5 – (Left) John Williams
Slide 7 – (Left) Source Undetermined
Slide 8 – Fig. 1-6 Granger, D, *et al. Clinical Gastrointestinal Physiology*. W.B. Saunders, Philadelphia, PA; 1985: 12.
Slide 9 – Source Undetermined
Slide 10 – John Williams
Slide 12 – Fig. 1-2 Granger, D, *et al. Clinical Gastrointestinal Physiology*. W.B. Saunders, Philadelphia, PA; 1985: 7.