MEDICINE 438's GITPHYSIOLOGY ECTURE I: General Principles of GIT Physiology



OBJECTIVES

- Physiologic Anatomy of the Gastrointestinal Wall
- The General/specific Characteristics of Smooth Muscle
- Smooth muscle cell classifications and types of contraction
- Muscle layers in GI wall
- Electrical Activity of Gastrointestinal Smooth Muscle
- Slow Waves and spike potentials
- Calcium Ions and Muscle Contraction
- Neural Control of Gastrointestinal Function-Enteric Nervous System (ENS)
- Differences Between the Myenteric and Submucosal Plexuses
- Types of Neurotransmitters Secreted by Enteric Neurons
- Autonomic Control of the Gastrointestinal Tract
- Hormonal Control of Gastrointestinal Motility
- Functional Types of Movements in the GI Tract
- Gastrointestinal Blood Flow (Splanchnic Circulation)
- Effects of Gut Activity and Metabolic Factors on Gastrointestinal Blood Flow



Term baby boy born to a 29 year old G2P1+ 0 by NSVD found to have features of Down's syndrome. At 30 hours of age Baby was feeding well but didn't pass meconium. On examination abdomen distended. Anus patent in normal position. During PR examination passed gush of meconium.

Diagnosis: Hirschsprung disease.

It is a developmental disorder characterized by the absence of ganglia in the distal colon, resulting in a functional obstruction.



Lecture One









- \star To achieve this function it requires:
- **1** Movement of food through the alimentary tract (motility).
- **2** Secretion of digestive juices & digestion of the food.
- **3** Absorption of : 1. Water 2. Various electrolytes 3. Digestive products.
- 4 Circulation of blood through the gastrointestinal organs to carry away the absorbed substances.





Functions of the GI System



The sedentary human body requires

 ≈ 30 kcal/Kg BW per day.



The food we consume is not in a form that can be directly absorbed by the small intestine.

Dietary nutrient	Consumed form	Absorbed form
Fat (lipids)	Triglycerides	Fatty acidsMonoglycerides
Proteins	 Proteins Large peptides	Amino acids
Carbohydrates	 Starch Disaccharides Monosaccharides 	

Functions of the GI System



FOOTNOTES

Check further readings, no. 1. 1.

Functional Anatomy of the Wall of GIT

 \star The anatomy of the wall varies but there is a common general theme.



The General Characteristics of Smooth Muscle

★ The role of 2 .. Cerebellum lecture attack.

2 Main muscle layers	2 Muscle classification	2 Types of contraction
1. Longitudinal Smooth Muscles	1. Unitary (single-unit)	1. Phasic (rhythmical)

★ Contraction:

- Expands the lumen.
- Shortens the segment.
- ★ innervated by enteric nervous system (ENS), and mainly by Excitatory motor neurons.
- ★ Ca⁺² influx from outside is important in their activity.

2. Circular Smooth Muscles

★ Contraction:

- Reduces the diameter of the lumen
- Increases the length.
- innervated by ENS, both excitatory & inhibitory motor neurons.
- ★ Intracellular release of Ca⁺² is more important.
- ★ Thicker and more powerful
- ★ More gap junctions

★ Contracts

- in the absence of neural or hormonal influence.
- in response to stretch.

★ Examples:

- Stomach & intestine.
- ★ Cells are electrically coupled via gap junctions.

2. Multi-unit

★ Does not Contract

- in the absence of neural or hormonal influence.
- in response to stretch.

★ Examples:

- Esophagus & gall bladder, iris and constrictor pili.

Smooth muscle cells contract <u>rhythmically</u> or intermittently.

Periodic contractions followed by relaxation

★ Example: Walls of the GI tract.

- Gastric antrum
- Small intestine
- Esophagus.

2. Tonic Check further readings, no. 2. Smooth muscle cells continuously active maintaining a "tone"

➤ Continuous partial contraction.

★ Examples:

- sphincters:
- Lower esophageal
- Ileocecal
- Internal anal
- vascular & respiratory smooth muscle
- Orad region of the stomach

★ Caused by:

- Repetitive spike potentials.
- Hormones.
- Continuous entry of Ca⁺² ions (not associated with changes in membrane potentials)
- Not associated with slow waves (often lasting several minutes or hours).

Examples of the Different Types of Smooth Muscle



Figure 1-7

Figure 1-8

(b) The arrangement of the fibers causes the

Contractile Mechanism of Smooth Muscle

(a) Actin and myosin are loosely arranged around the periphery of the cell, held in place by protein dense bodies.





Molecular Basis of Smooth Muscle Contraction

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↑ Intracellular ca<sup>+2</sup> concentration by:
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- Entry to cell
- Ca⁺² release from sarcoplasmic reticulum
- **2** Ca^{+2} binds to calmodulin (CaM)
- **3** Ca⁺²-calmodulin activates Myosin Light Chain Kinase (MLCK)
- **4** MLCK phosphorylates light chains in myosin heads and increases myosin ATPase activity
- 5 Active myosin crossbridges slide along actin and create muscle tension.





Figure 1-10

How Does Smooth Muscle Contraction Stop ?









The Specific Characteristics of Smooth Muscle in Gut

1- Action potentials



FOOTNOTES

1. Varicosities are the swellings of nerve fibers that contain the neurotransmitter prior to its release from vesicles. The term is used more with smooth muscle fibers. Whereas in case of skeletal muscles we refer to those interactions as neuromuscular junctions (NMJ).

2 – Electrical activity

Slow (myogenic) Waves¹

Definition:

Rhythmic oscillating depolarization and repolarization in the resting -membrane potential with unknown cause.

Continual.

Intrinsic.

Slow.

Origin:

Interstitial cells of Cajal (ICC)

- It's the GI pacemaker.
- Abundant in myenteric plexuses (between smooth muscle layers)
- form a network with each other
- synaptic-like contacts to smooth muscle cells.

Function:

Determine the rhythm of GI contraction

Features:

- No Ca entry (only Na)
- Not action potentials (because it's below threshold)
- No muscle contraction
- Intensity : 5–15 mV
- Frequency 3-12/min
 - Ranges in different parts of GI tract
 - Stomach: 3/min
 - Duodenum: 12/min
 - Ileum: **8-9**/min



Spike potentials¹

True Action potentials

Generation:

- Automatically when the resting membrane potential becomes more positive <-40 mV (Resting membrane potential : -50 - -60 mV)
- At the peaks of slow waves.
- Frequency:
- 1-10 spikes/min

Duration:

Each spike lasts as long as **10–20 ms** 10-40 times as long as the action potentials in large nerve fibers

Direct Relation with slow waves:

slow wave potential (above threshold) $\rightarrow \uparrow$ frequency of the spike potentials

FOOTNOTES

It's important to point out that action potentials only occur when these slow-wave potentials are superimposed by excitatory neurotransmitters released 1. by nerve endings. Which means that slow-wave potentials provide the threshold required for excitatory neurotransmitters to fulfill their activities.

2 – Electrical activity

Changes in Voltage of the Resting Membrane Potential.

Factors depolarize the membrane (make it more excitable)	Factors hyperpolarize the membrane (make it less excitable)
 1-Muscle stretch¹. 2- Acetylcholine (parasympathetic stimulation). 3- Specific GI hormones. 	Sympathetic stimulation Epinephrine (mainly). Norepinephrine.
With parasympathetic input, the membrane at the plateau of the slow wave depolarizers all the way to threshold; action potentials occur "on top of" the slow wave, and these set off contractions. The contraction / tension follows slightly after the electrical response.	$\int_{1}^{0} \int_{-40}^{0} \int_{1}^{0} \int_$
Structures	Slow Slow





Stimulation by

Slow waves

FOOTNOTES

To conceptualize this, just beneath the epithelium there are mechanosensitive sensory neurons that can communicate with ENS in 1. response to stretch to initiate contraction.



3- Syncytial function

Syncytium: when an action pote muscle mass, it gen muscle.	ential is elicited anywhere wi erally travels in all direction	thin the s in the
Muscle fibers: Length: 200 - 50 Diameter: 2 - 10 Arrangement: Bu 	0 μm. μm. indles.	
Muscle bundle : 1000 parallel fibe Gap junctions com 	ers. nnect muscle fibers.	
Control of GI Fur	nction	
Neural	Hormonal	GI contents
1. Enteric Nervou	s system:	

- The nervous system of GI tract.
- Lies entirely in the wall of the gut.
 - esophagus \rightarrow anus.
- Has as many neurons as spinal cord (~ 100 million).
- Its function is largely independent of the extrinsic NS "mini-brain"
 - Parasympathetic & sympathetic systems¹ Can greatly enhance or inhibit
 - gastrointestinal functions.
- The sensory nerve endings send afferent fibers to:
- 01. Plexuses of the enteric system .
- **02.** Prevertebral ganglia (sympathetic NS).
- **03.** Spinal cord.
- 04. Vagus nerves (80% afferent).
- \rightarrow To the brain stem (Medulla).
 - Vagovagal reflexes
- \rightarrow Elicit local reflexes within the gut wall.



FOOTNOTES

1. Note that parasympathetic nervous system acts via preganglionic neurons, meaning it has to synapse within the the ENS to induce any physiological effect, in-order for the preganglionic to become postganglionic. Whereas sympathetic nervous system can act directly and indirectly, sympathetic nerves can also inhibit ACh release by acting on vagal nerve endings. This contributes to their inhibitory function.

Control of GI Function		
Neural Hormo	onal GI contents	
••••••		
. Enteric Nervous system:		
2 maii	n plexuses	
Myenteric "Auerbach's"	Submucosal "Meissner's"	
Outer	Inner	
between longitudinal & circular muscle layers.	In submucosa	
Found throughout the GIT	Only in small & large intestine	
Controls GI <u>movement</u> . "Motility"	Controls <u>secretions</u> & local <u>blood flow</u> .	
 Tonic contraction. Intensity and rate of rhythmical contractions. Velocity of conduction of excitatory waves along the gut wall. 	 Controls : 1. local intestinal secretion. 2. local absorption. 3. local contraction of submucosal muscle. → various degrees of enfolding of the GI mucosa. 	
Consists mostly of a linear chain of many interconnecting neurons.		
Has excitatory & inhibitory motor neurons.		





Figure 41-3 Schematic representation of the ENS. A, The submucosal (or Meissner's) plexus is located between the muscularis mucosae and the circular muscle of the muscularis externa. The myenteric (or Auerbach's) plexus is located between the circular and longitudinal layers of the muscularis externa. In addition to these two plexuses that have ganglia, three others-mucosal, deep muscular, and tertiary plexus-are also present. B, The ENS consists of sensory neurons, interneurons, and motor neurons. Some sensory signals travel centrally from the ENS. Both the parasympathetic and the sympathetic divisions of the ANS modulate the ENS. This figure illustrates some of the typical circuitry of ENS neurons. Figure 1–19

Control of GI Function



• Ach.	
 ★ Release water, electrolytes and mucus from crypts of Lieberkuhn¹. 	
Afferent Sensory Nerve Fibers from the Gut	1.1
Cell bodies location:	1.1
 Enteric nervous system. 	
 Dorsal root ganglia. 	1.1
• Stimuli	
i. Irritation of the gut mucosa.	1.1
ii. Excessive distention of the gut.	1.1
iii. Presence of specific chemicals in the gut.	
 Type of signal transmitted 	1.1
- Excitatory.	1.1
– Inhibitory.	1.1
	1

FOOTNOTES

1. Crypts of Lieberkuhn: Remember that the gut mucosa is far-away from smooth, it is invaginated into "pits", with mucus cells at the surface. These pits are called crypts of lieberkuhn, check further readings for more.





- 1. Celiac
- 2. Superior mesenteric
- 3. Inferior mesenteric



Figure 1-20

3. Parasympathetic nervous system:

- Vagus nerves (cranial division) innervate:
- Esophagus.
- Stomach.
- Pancreas.
- Intestines down to the first half of the large intestine.
- Pelvic nerves (sacral division) innervate:
- Distal half of the large intestine.
- Anus.
- (To execute the defecation reflexes).
- Postganglionic neurons are located mainly in the myenteric and submucosal plexuses.
- Stimulation causes general increase in activity of the enteric nervous system.



Control of GI Function



Hormone	Site of action	Stimuli	Actions
Gastrin	G cells - Antrum - Duodenum - Jejunum	 Protein. Distention of the stomach. Vagal stimulation (GRP). Acid (inhibits release). 	 Stimulates: Gastric H+ secretion. Growth of gastric mucosa.
Cholecystokinin (CCK)	I cells - Duodenum - Jejunum - Ileum	 Protein. Fatty acids. Acids. 	 Stimulates: Pancreatic enzyme secretion. Pancreatic HCO-3 secretion. Gallbladder contraction. Exocrine pancreas growth. Relaxation of the sphincter of Oddi.¹ Inhibits: Gastric emptying
Secretin	S cells - Duodenum - Jejunum - Ileum	 Acids. Fat. (in the duodenum) 	Stimulates: • Pepsin secretion. • Pancreatic HCO -3 secretion. • Biliary HCO -3 secretion. • Exocrine pancreas growth. Inhibits: Gastric H+ secretion
Glucose-Dependent Insulinotropic Peptide (GIP)	K cells - Duodenum - jejunum	 Protein. Fatty acids. Oral glucose. 	Stimulates: Insulin secretion (from pancreatic β cells)Inhibits: Gastric H+ secretion
Motilin	M cells - Duodenum	 Fat. Acid. Norvo 	Stimulates: Gastric motility.



INCLVC.

Intestinal motility



FOOTNOTES

1. Sphincter of Oddi: most of food absorption occurs in jejunum, and duodenum serves in digestion of food before absorption in jejunum. This digestion is helped by pancreatic and biliary secretions that contain many enzymes and are collected in a common duct that empties into the duodenum, the sphincter for this duct is the sphincter of Oddi.





- required for defecation:
- Colon.
- Rectum.
- Abdomen.





Functional Types of Movement in the GIT

Propulsive (Peristalsis)	Mixing (segmentation)
Progressive wave of contraction & relaxation. To push food forward	Non-propulsive segmental contractions. To break food into smaller pieces
Organizes propulsion of material over variable distances within the GI lumen.	 ★ Blend different juices with the chime. ★ Bring products of digestion in contact with absorptive surfaces.
 Propulsive (upstream) segment Contraction (circular Muscle) Relaxation (longitudinal Muscle) Receiving (downstream) segment Contraction (longitudinal Muscle) Relaxation (circular Muscle) 	 ★ Propulsive segment. - Contraction (circular Muscle) ★ Receiving segment. - Relaxation (circular Muscle)
 ★ Stimulus: distention. Others: - Chemical irritation. 	

- Physical irritation.

 \star Myenteric plexus is important.

- ★ Atropine (cholinergic blocker) depresses propulsion.
- (c) **Peristaltic contractions** are responsible for forward movement.

E seconds later

5 seconds later Figure 1–26 creates segments along the intestine.



Figure 1-27

(d) Segmental contractions are responsible for mixing.

Circular muscles alternate contracting and relaxing, which creates segments along the intestine.

Functional Types of Movement in the GIT

Peristaltic Reflex and the "Law of the Gut"

When a segment of the intestinal tract is excited by distention and initiates peristalsis:

The contractile ring

- 1. begins on the **Orad** side of the distended segment.
- 2. Moves toward the distended segment.
- Pushing the intestinal contents in the anal
 (Caudad) direction for 5 10 cm before dying out.



Lecture One

Figure 1-28

Does the Bowel Move in the Fasting State? During fasting between periods of digestion, the pattern of electrical and motor

During fasting between periods of digestion, the pattern of electrical and motor activity in GI smooth muscle becomes modified

Migrating motor complexes (MMC):

Definition:

Cycles of motor activity (periodic gastric contractions).

Location:

Migrate from the stomach to the distal ileum.

Occurrence: Every 90-120 min

Mediator:

Motilin

- 22–amino acid peptide.
- Not a member of the gastrin-CCK or the secretin-glucagon family.
- Secreted from the upper duodenum.
 believed to increase gastro-intestinal motility .
 initiate MMC.

Function:

Clear the stomach & small intestine of any residue remaining from the previous meal. its absence has been associated with gastroparesis, Intestinal pseudo-obstruction and small intestinal bacterial growth.

Characters:

Increase in

- Gastric secretion.
- Bile flow.
- Pancreatic secretion .

4 phases:

Phase I

Quiescent period Phase II Irregular electrical and mechanical activity Phase III Burst of regular activity Phase IV Declining activity which merges with the next Phase I.



GI Blood Flow "Splanchnic Circulation"



Control of GI Blood flow

Neural

Gut activity

Parasympathetic stimulation ↑ Local blood flow ↑ Glandular secretion Sympathetic stimulation intense vasoconstriction of the arterioles ↓ Local blood flow (greatly) ★ The local metabolic vasodilator mechanisms override the sympathetic effects, returning the normal blood flow to GI muscle and glands.

FOOTNOTES

1. Sinusoids are minute vessels that are lined by phagocytic cells called, Kupffer cells, these help in phagocytosis of microorganisms helping us avoid states like septicemia.



★ From dr's slides



Smooth muscle cells respond to slow wave depolarisations with increased Ca²⁺ channel open probability Smooth muscle cells Electronic conduction of slow waves Varicosity Neurotransmitters and hormones condition the smooth muscle syncytium Intramuscular ICC to generate the desired Enteric response motorneurone

FURTHER READINGS

- 1. How the gastrointestinal system influences the immune system? This is done mainly through the gut microbiome. The gut microbiome help boost T-cell numbers early in life, they feed us with a list of antigens that we should be tolerant to, studies even proved this germ-free mice and then after they were injected with a single microbe, Bacteroides fragilis. Bacteroides fragilis in the gut had an antigen that boosted T-cell number early in-life and even protected against diseases like multiple sclerosis! People born with C-section have abnormal microbiome, their immune system is tolerant to less antigens and easily triggers inflammation, the consequence is that people with abnormal gut microbiome are more prone to bronchial asthma.
- 2. Mechanism of tonic contraction: From what we know from mechanisms of contraction, myosin binds to actin which forms what we call a "cross-bridge formation", the myosin then consequently pulls actin towards the center or belly of the muscle, the muscle shortens then and contracts. In smooth muscle cells, during the time in which myosin pulls the actin, a certain regulatory protein called myosin-light chain can get dephosphorylated, if this protein gets dephosphorylated during contraction then the muscle will remain contracted with constant force, **this is called the latch mechanism for muscle contraction**, and is the basis for tonic contraction in smooth muscle cells including sphincter, this process does not require much ATP. Allowing sphincters to function optimally.





3. Crypts of lieberkuhn: The surface of the intestinal mucosa is highly folded, forming the gland formation seen below. The pit or hole of this folding is called a "crypt". We can see in the first figure that there is surface mucus cells which are columnar, this is seen below the esophagus in GI tract, remember that it is lined by stratified squamous. Within the neck of this pit we see mucus neck cells, along with stem cells. Stem cells then can differentiate and migrate below to form parietal, chief or ECL cells, they lie in the depth of the pit among others. This whole structure is called a gland.





QUIZ



1. Which hormone is released by the presence of fat and protein in the small intestine and has a major effect in decreasing gastric emptying?

- A) CCK
- B) Gastrin
- C) Motilin
- D) Secretin
- 2. Which one of the following GI reflexes inhibit stomach motility and secretion?
- A) Gastrocolic reflex
- **B)** Enterogastric reflex
- C) Colonoileal reflex
- D) Intestino-intestinal reflex
- 3. Myenteric plexus of the wall of the stomach is present:
- A) In the serosa
- B) Between the middle circular muscle layer and the mucosa
- C) Between the outer longitudinal muscle layer and circular muscle layer
- D) In the muscularis mucosa
- 4. Cholecystokinin is synthesized and released by
- A) S cells
- B) G cells

C) D cells D) I cells

- 5. Gastric pepsin helps in digestion of
- A) carbohydrate
- B) Lipids
- C) Iron
- D) Proteins

SHORT ANSWER QUESTIONS

- 1. List three factors that cause increase blood flow during GI activity.
- What are the plexuses of the enteric nervous system & their functions?
- 1.
- Gastrin
- Bradykinin
- Decrease oxygen concentration
- 2.
- Myenteric plexus: controls GI motility.
- Submucosal plexus: controls secretions & local blood flow.
 - ANSWER KEY: A, B, C, D, D



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