GI Physiology Series
GI Motility

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What is GI Motility
• Gastrointestinal (GI) motility is defined as the coordinated contractions and relaxations of the muscles of the GI tract necessary to move contents from the mouth to the anus
• Peristalsis is the result of a series of local reflexes
• Contraction of intestinal muscle above an intraluminal stimulus associated with simultaneous relaxation of muscle below the stimulus
• Starling’s Law of Regulators of motility underlie excitatory and inhibitory neurons and form the basis for Starling’s law of the intestine
• Luminal stimulation results in ascending contraction and descending relaxation, facilitating bolus transport. This sequential enteric reflex pattern results in the phenomenon of peristalsis of the Intestines

Mechanisms of Peristalsis
• Gastrointestinal peristalsis is a pattern of alternative contraction and relaxation of circular and longitudinal muscles in the intestinal wall resulting in specific activity:
  • Segmental contractions
  • Propulsive or propagative contractions

  • Segmental contraction result in
    - Mixing of luminal contents with intestinal secretions to drive digestion
    - Exposure of mucosal surface to luminal contents to drive absorption
  • Propagative contractions
    - Movement of residual luminal contents aborally as digestion progresses
    - Elimination of indigestible and non absorbable contents
  • Tonic contractions
    - Noted at various sphincteric regions where the circular muscles are tonically contracted at rest resulting in luminal occlusion.
• These contractions are mediated by local reflexes, by a process of receptive relaxation associated with luminal distention followed by contraction propelling contents
• There are specific set patterns of motility noted in healthy individuals along the different parts of the GI tract.

Esophageal Motility
• Esophageal longitudinal muscle may also play a role in peristalsis
• Proximal 1/3rd Striated Muscle : Controlled by motor neurons from the central nervous system (CNS)
• Distal 2/3rd Smooth Muscle : Under local neuronal control with CNS input
• UES relaxation is seen before a rise in pressure from swallowed bolus that then travels distally along the esophageal body.
• A proximal pressure trough is noted at the transition point of striated to smooth muscle in the proximal 3rd of the esophageal body.
• A distal pressure trough is noted were esophageal body transitions to the gastro esophageal junction.
• A deglutitive relaxation window that begins with 1-2 seconds of the UES contraction and remains open until bolus transfer into the gastric lumen is noted at the esophagogastric junction.

Esophageal Topography Scores
• Younger patient age and shorter size correlated significantly with greater IRP4s (p < 0.05), shorter DL (p < 0.001) and smaller BS (p < 0.05).
( Neurogastroenterol Motil. 2014 Jul 23)

Achalasia Subtypes
• Classification of achalasia based on high resolution manometry topography.
• Achalasia is defined as variable loss of esophageal body propagative peristalsis with non relaxation of the lower esophageal sphincter.
  - Type I shows no measurable pressures along the esophageal body along with non-relaxation of the esophago-gastric junction
  - Type II shows simultaneous esophageal pressurization and non-relaxation of the esophago-gastric junction
  - Type III shows high pressure simultaneous contraction of the distal esophageal body with and non-relaxation of the esophago-gastric junction

Motility Patterns in Esophageal Smooth Muscle Disorders
• Conventional manometry tracing of esophageal motility disorders noted in comparison to normal tracing on the left.
• Scleroderma tracing shows progressive loss of amplitude of contractions on the esophageal body and LES.
• Type I achalasia shows decreased amplitude of esophageal body distally with non relaxing (sometimes hypertensive with pressures >400mmHg) lower esophageal sphincter
• Diffuse esophageal spasm is noted with simultaneous and sustained contraction of distal esophageal body and hypertensive LES leading to dysphagia and chest pain with swallow
• Nutcracker esophagus is noted with propagative but sustained esophageal contractions and a hypertensive LES leading to no dysphagia but chest pain with swallow

Gastric Motility
  • Proximal 2/3:
    o fundus and body
    o reservoir, expands with infusion of food
  • Distal 1/3:
    o antrum and pylorus
    o peristaltic, muscular, phasic powerful contractions
    o triturates food and regulates movement into the duodenum
  • **Receptive relaxation**
    o Triggered by swallowing
    o Smooth muscles in the fundus and body relax
    o Mediated by the gastric enteric nervous system
  • **Peristaltic waves**
    o Waves of contraction, 3/min, regulated by gastric pacemaker, Interstitial cells of Cajal
    o Each wave proceeds from the body toward the antrum
    o Amplitude of contraction determined by neural and hormonal input
    o Mix and break down food into small particles (1-7 mm)

Migrating Motor Complexes
  • 2 functional parts: Similar in overall pattern with mild differences that may account for variations in digestive roles
  • Proximal – duodenum and jejunum. Known small bowel motility patterns are based on proximal small bowel studies
  • Increased frequency in jejunum at night
  • Role in keeping proximal gut relatively sterile
  • Distal – ileum. Less intense and propagative
  • Lower frequency, slower propagation velocity, shorter distance of propagation
  • Possibly slowing and enhancing nutrient absorption.
  • Migrating motor complex contractile pattern repeats every 60 min – 6 hrs during inter-digestive period
Purpose of MMC
- Clear residual chyme from the intestinal lumen
- Prevent bacterial overgrowth in small intestine
- Mediator is motilin

MMC
- Phase I – Interdigestive State
  - Quiescent to infrequent low amplitude non propagative contraction.
  - Resting phase to recover muscle strength
- Phase II – Increasing activity (Irregular activity)
  - Similar to fed state, but last 30-60 minutes. Random, variable amplitude, sometimes propagating, sometimes not propagating
- Phase III – Clustered contractions (Intense peristalsis)
  - Highest amplitude of normal small bowel contraction 15-40 mm Hg
  - 10-20 minutes in duration
  - Propagating and propulsive housekeeping contractions
  - Occur every 60-90 minutes
  - Inhibited by fed state

Colonic Motility Patterns
- High amplitude propagative contractions (HAPCs):
  - Infrequent event in humans
  - Average 0-6 times/day
  - 80 - 120 mm Hg
  - Constant when recorded from different colonic segments
  - Propagate oroaborally
  - Associated with borborygmus and defecatory stimulus,
  - The diurnal and nocturnal patterns directly related to physiologic events (sleep, physical activity and eating)
  - Decrease with age (infants 1 /1-2 hr)
- Low Amplitude Propagated Contractions (LAPCs):
  - Poorly studied
  - ~60 clusters/ 24hr
  - 5 – 40 mm Hg
  - Involved in transport of liquid and gaseous colonic contents

Colonic Propulsive Activity
- [A] Colon before entry of barium sulfate
- (B) Barium enters proximal ascending colon, showing hastrula
- (C) As more barium enters, the hastra disappear from a portion of the ascending and transverse colons, and a contraction begins in this area
  - (D) The contraction has moved a portion of the barium into the caudad transverse colon
  - (E) Haustra return
GastroColic Reflex
- Reproducible physiologic response
- Colonic activation within 1–3 minutes up to 1 hour following a meal
- Response lasts up to 3 hours in healthy subjects
- Most active at a younger age
- Chiefly segmental contractions but LAPCs and HAPCs also increase

Postprandial colonic motility is influenced
- caloric content - greater the calories better the response
- meal composition, fat and carbohydrates stimulate; Protein (amino acids) inhibit

Anorectal Motility - Defecation
Two phased:
- **Involuntary first phase**
  - colonic contents are transported toward the rectum,
  - increased rectal distention and pressure,
  - relaxation of internal anal sphincter
- **Voluntary second phase**
  - increased intra-abdominal pressure,
  - pelvic floor (puborectalis and levator ani) relaxation and descent,
  - straightening of the anorectal angle,
  - relaxation of external sphincter
  - expulsion of contents

Rectoanal Inhibitory Reflex (RAIR)
- In this high resolution topography, rectoanal inhibitory reflex is demonstrated.
- The basal sphincter tone is generates a pressure topography as shown. The anal canal length is constituted by both the external and internal anal sphincter. With the rectal distention, by distending a balloon in the rectum, local neural reflexes are triggered and there is involuntary relaxation of the internal anal sphincter.
- In the image on the right, the external sphincter remains tonically contracted. The external sphincter is then relaxed voluntarily by the individual when he chooses to complete defecation.
- In the image on the left, the external anal sphincter is also relaxed simultaneously. This may typically be seen in child that has not been toilet trained yet.
Regulation of GI Motility

- Hormones and neurotransmitters are the dominate regulators of GI smooth muscle activity and motility
- The receptors involved in motility are located on smooth muscle cells and components of the enteric nervous system and neuronal structures extrinsic (outside of) the gut (Spencer 2001)
- Involves the intrinsic (enteric nervous system) as well as extrinsic nerves (vagus, splanchnic and pelvic nerves)
- Inhibitory signaling molecules (which are released in response to inhibitory stimuli) are VIP, serotonin, NO and pituitary adenylate cyclase activating polypeptide (PACAP). These molecules exert a relaxing effect on gut muscles
- Excitatory signaling molecules are tachykinins, acetylcholine and serotonin. These molecules cause contraction of GI tract muscles
- Reflex activation of myenteric neurons by stimuli, such as stretch or mucosal stimulation, leads to relaxation in the caudad intestine and contraction in the orad intestine (Kunze and Furness 1999, Olsson and Holmgren 2001)

Interstitial cells of Cajal –

- The interstitial cells of Cajal (ICC) are a specialized group of cells in the intestinal wall that are involved in the transmission of information from enteric neurons to smooth muscles cells.
- ICCs generate the basic electrical rhythm, or slow wave” activity, that is a consistent feature of GI smooth muscles
- Motilin and motilin receptor agonist such as erythromycin stimulate antral contractions, normally triggering phase III of the MMC.

Excitation Contraction Coupling Stimulating Peristalsis

- The rising phase of the action potential is caused by flow of ions through channels that conduct both Ca** and Na* and are relatively slow to open.
- The Ca** that enters the cell during the action potential helps initiate contraction.
- The extent of depolarization of the cells and the frequency of action potentials are enhanced by some hormones and paracrine agonists and by neurotransmitters from excitatory enteric nerve endings (e.g., acetylcholine and substance P).
- Inhibitory hormones and neuroeffector substances (e.g., vasoactive intestinal polypeptide and nitric oxide) hyperpolarize the smooth muscle cells and may diminish or abolish action potential spikes.
- The greater the number of action potentials that occur at the peak of a slow wave, the more intense the contraction of the smooth muscle.
- Between the trains of action potentials, the tension developed by GI smooth muscle falls, but not to zero. This nonzero resting, or baseline, tension of smooth muscle is called tone.
- The tone of GI smooth muscle is altered by neuroeffectors, hormones, paracrine substances, and drugs.
Neural Control of Defecation

- Haustral contractions are slow contractions that occur about every 30 minutes and last approximately 1 minute. They are stimulated by stretch when food remnants fill the haustra.
- Mass movements are long, slow moving, powerful contractions that move over the colon 3 or 4 times per day, typically after meals. This gastrocolic reflex accompanies the gastroileal reflex stimulated by gastrin release when the stomach receives food.
- In addition to these movements some segmentation occurs in the descending and sigmoid colon to increase water absorption before mass movements propel the feces into the rectum.
- Feces forced into the rectum by mass movements stretch the rectal wall and initiate the defecation reflex.
- Distension of the recto-sigmoid region with fecal matter results in awareness of the urge to defecate, an *intrinsic defecation reflex*.
- A *strong, spinal reflex* initiated by the parasympathetic motor (efferent) fibers stimulates contraction of the rectosigmoid colon and internal anal sphincter inhibitory action.
- The smooth internal *anal sphincter muscle* maintains a tonic contraction during continence, due to its sympathetic fibers from the *lumbar medulla* (through hypogastric nerves and the inferior mesenteric ganglion).
- The muscle relaxes due to its parasympathetic, cholinergic fibers in the pelvic splanchnic nerves (S2-S4).
- The strong spinal reflex produces relaxation of the smooth muscles of the internal anal sphincter and contraction of the striated muscles of the external anal sphincter (innervated by somatic fibers in the pudendal nerve) inhibiting the reflex and causing *receptive relaxation*.
- If it is convenient to defecate, Voluntary motor neurons are inhibited, allowing the external anal sphincter to relax.

Hormonal Regulation of Motility

- The hormonal regulation occurs postprandially.
- The postprandial endocrine response includes release of insulin, neurotensin, cholecystokinin (CCK), gastrin, glucagon-like-peptides (GLP-1 and GLP-2), glucose-dependent insulintropic polypeptide, but not motilin or somatostatin (Medhus *et al.* 1999).
- CCK:
  - Stimulates contractions of primarily the circular layer of the intestines and gall bladder.
  - Neurally mediated relaxation of muscle cells in the sphincter Oddi
  - Exogenous CCK relaxes the LES and the stomach, while endogenous CCK relaxes the colonic muscle (Scarpignato 1996)
- Histamine:
H1 receptors mediate contraction and H2 receptors mediate relaxation with the net effect of contraction, reflecting the dominant influence of H1 receptors. (Keinke et al. 1986)

- Corticotropin Releasing Factor (CRF):
  - slows gastric emptying and small intestinal transit,
  - increases colonic transit and defecation in healthy volunteers and causes an exaggerated colonic motility response in IBS patients (Monnikes et al. 2001)

- COX-2 Inhibitors:
  - induce duodenal motility in rats, suggesting Prostaglandins exert a tonic inhibitory action on duodenal motility (Nylander et al. 2001)

- Galanin:
  - causes relaxation of the ileum via action on myenteric neurons (Ren et al. 2001)

- Gastrin:
  - relaxes the fundus and increases gastric wall compliance (Mearadji et al. 1999)

- GLP-1 and GLP-2:
  - inhibit fasting and postprandial gastric and antroduodenal motility and stimulate tonic and phasic contractile activity of the pylorus

- Ghrelin:
  - stimulates gastric contractility via a vagal pathway (Chen et al. 2001)
  - Interleukin-1 beta:
    - decreases ACh-induced intestinal contraction in a VIP-dependent manner (Aube et al. 2001)

Embryonic Development

- The airway and lung buds, pharynx, esophagus, stomach, and diaphragm are all derived from the primitive foregut and share similar control systems.
- The epithelial lining of the developing alimentary canal forms from the endoderm with the rest of the wall arising from the mesoderm.
- At 4 weeks, the stomach is a fusiform tube with its dorsal side growth rate greater than its ventral side, creating greater and lesser curvatures, with left vagus being anterior and right vagus posterior in position.
- The anterior most endoderm touches the depressed area of the surface ectoderm where the membranes fuse to form the oral membrane and ultimately the mouth.
- The end of the hindgut fuses with an ectodermal depression, called the proctodeum, to form the cloacal membrane and ultimately the anus.
- 8 weeks the alimentary canal is a continuous tube stretching from the mouth to the anus.
- 10 weeks gestation, the esophagus and stomach are in proper position, with circular and longitudinal muscle layers and ganglion cells in place.
• By 11 weeks ability to swallow develops; 18 to 20 weeks: sucking movements appear
• By term the fetus can swallow and circulate nearly 500 ml of amniotic fluid. Swallow-induced peristaltic activity begins in fetal life

Autonomic Nervous System Regulation of GI Motility
• The parasympathetic preganglionic input is provided by cholinergic neurons and elicits excitatory effects on gastrointestinal motility via nicotinic and muscarinic receptors
• Sympathetic input occurs through postganglionic adrenergic neurons

Norepinephrine and Acetylcholine
• Acetylcholine:
  - Synthesized in cholinergic neurons
  - Principal regulator of gastrointestinal contraction
  - Acetylcholine binds to postsynaptic muscarinic and/or nicotinic receptors
• Norepinephrine:
  - One of the primary catecholamine neurotransmitter of ENS, synthesized from tyrosine and bind to adrenergic receptors
  - Norepinephrine signaling is terminated by intracellular monoamine oxidase or by rapid reuptake by an amine transporter
  - The actions of adrenergic receptor stimulation regulate smooth muscle contraction, intestinal blood flow, and gastrointestinal secretion

Serotonin
• The gastrointestinal tract contains > 95% of total body serotonin
• It is synthesized from tryptophan, an essential amino acid, and is converted to its active form in nerve terminals
• Seven different serotonin receptors in the enteric neurons, enterochromafin cells and gastrointestinal smooth muscle cells – 5HT1 to 5HT 7
• Causes smooth muscle contraction via stimulation of cholinergic neurons
• Causes relaxation by stimulating inhibitory nitric oxide neurons
• Persitaltic reflex is initiated vis 5-HT4 receptors and mediated sensation via 5-HT3 receptors

Nitric Oxide
• Nitric oxide (NO) is a major inhibitory noradrenergic, non-cholinergic neurotransmitter in the GI tract
• Nitric oxide synthesized from arginine via nitric oxide synthase
• Diffuses across plasma membranes into smooth muscle cells.
• NO binds and activates guanylyl cyclase, converting GTP to cGMP which causes smooth muscle relaxation.
• Nitric Oxide regulates:
- Muscle tone of the lower esophageal sphincter, pylorus, sphincter of Oddi, and anus
- Accommodation reflex of the fundus and the peristaltic reflex of the intestine

Enteric nervous system (ENS): Gut’s own nervous system
- Reflexes triggered by local sensory inputs with the integrative ability of the ENS allows assimilation of information from the muscle and mucosa to determine the appropriate gut response
- The ENS is usually formed from two major plexuses: the myenteric plexus mainly regulating muscle activity and the submucosal plexus mainly regulating mucosal functions
- Exhibits programmed functions (e.g., MMC, peristalsis)
- Contains multiple neurotransmitters including all from CNS
- The ENS contains about 100 million nerve cell bodies, this is the second largest accumulation of nerve cells, after brain
- Actions modified by vagal and sympathetic extrinsic nerves

Visceral Pain:
- arises from the internal organs of the body
- Diffuse localization
- Unreliable association with visceral pathology
- Referred sensations
- Strong autonomic and emotional responses may be evoked with minimal sensation

Hyperalgesia:
- tonic increased down regulation from higher brain centers
- **Hyperalgesia** - a painful stimulus leads to a response that is greater in intensity and duration than normal
- **Allodynia** - a pain response by a stimulus that does not normally produce pain

The biopsychosocial model of IBS
The biopsychosocial model of disease in functional disorders of the gastrointestinal tract is intimately related to psychological stressors or early life events that result in changes in the intestinal motility and or secretion and sensation predisposing to symptoms such as abdominal pain, nausea, satiety, changes in defecation and dyspepsia.
Brain-Gut Interaction

- Acute clinical or subclinical infectious trigger leads to mucosal changes in response to inflammatory triggers.
- These changes lead to dysmotility and hypersecretion causing significant psychological and physical distress.
- Brain gut axis mediated visceral response occurs and sets up a cycle of irritable or pain predominant functional bowel disorders.