

# GI Physiology

## Chapter 1

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# Regulation

- Regulated by hormones, paracrines, and neurocrines
- Specific criteria for each type
- Most are peptides in the GI tract

# Hormones

- Released into the general circulation and reach all tissues
- Exception is the BBB
- Specificity is a property of the target tissue
- 5 “established” GI hormones
- Candidate hormones

# Hormone requirements

- 4 steps
- 1: physiologic event, like a meal, must be demonstrated to provide the stimulus to one part of the digestive tract that alters the activity of another part
- 2: the effect must persist after all nervous connections are severed
- 3: from stimulus site, substance must be isolated that can be injected into blood and mimics effect of stimulus
- 4: that substance has to be identified chemically, structure confirmed by synthesis

# Paracrines

- Released from endocrine cells and diffuse to target tissue
- Effects limited by short distances of diffusion
- Can act on endocrine cells and cause hormonal response

# Neurocrines

- Located in nerves
- Released near target tissue and diffuses across a synaptic gap
- May stimulate release of hormones and paracrines

# Candidate hormones

- Chemically defined peptides that have significant actions in physiology or pathology by whose hormonal status has not been proved

# Discovery

- Secretin first by Bayliss and Starling in 1902
- Others followed
- Took many years to establish all 4 criteria for hormone status

# Chemistry

- Two basic families among the full “hormones”
- Gastrin/CCK
- Secretin/VIP/GIP/(glucagon)
- Regulatory signals and growth factors
- Most exist in two or more molecular forms (can have different half lives)

# Gastrin/CCK

- Last 5 c-terminal AA are identical in both
- Biologic activity of gastrin is maintained in last 4 AAs at c-terminal (1/6<sup>th</sup> activity)
- CCK-A receptor in gallbladder for CCK and CCK-B receptor in stomach for gastrin
- Cross receptor activity by not as potent
- Particular AAs and functional groups required for action of individual hormones (eg sulfated tyrosyl residue at position 7 of CCK)

# Secretin Family

- Secretin/VIP/GIP/glucagon
- Secretin has 27 AA, all needed for activity (no active fragments like with gastrin)
- GIP and VIP have 9 AA similar and pancreatic glucagon has 14 AA similar

# Distribution

- Located in endocrine cells scattered throughout the GI mucosa stomach to colon
- Difficult to study since cant cut them all out
- APUD (amine precursor uptake decarboxylation cells) members derived from neuroendocrine-programmed cells from embryonic ectoblast

# Distribution

- Gastrin in antral and duodenal mucosa
- Rest in duodenum and jejunum
- Some CCK and secretin in ileum

# Release

- Endocrine cells have granules at bases close to capillaries and microvilli at apical border to sample luminal contents
- Release granules in response to stimulus
- Intestinal releasing factors stimulate CCK release
- Releasing factors are inactivated by pancreatic enzymes like trypsin

# Actions

- Pure hormones have an effect on almost every target tissue (= receptors are present)
- Not always at physiologic dose
- Action should occur in response to endogenous hormone release by normal stimuli
- Guideline is a dose that produces 50% max response of primary action as administered at continuous infusion

# Gastrin

- Stimulated by protein, distention of the gastric antrum, and nerves
- Inhibited by acid
- Stimulates gastric acid secretion (most important regulator of acid secretion)
- ? Role in regulating LES (evidence = no)
- Trophic activity on small intestine, colon, and oxyntic gland of stomach (inc RNA, protein, DNA synthesis)

# Gastrin

- If loss of gastrin (eg antrectomy) then atrophy of above tissues
- Hypersecretion leads to hypertrophy/hyperplasia of acid secreting portion of stomach
- Stim growth of ECL cells
- Trophic effects counteracted by secretin
- Inh by secretin and glucagon

# Secretin

- Stimulated by acid (lesser extent by fat)
- Stimulates secretion of pancreatic fluid and bicarb
- Stim growth of exocrine pancreas
- Stim biliary secretion of fluid/bicarb
- Can inhibit gastrin stim acid secretion (?  
Importance in humans)
- Stim pepsinogen secretion from chief cells (?  
Physiologic)

# CCK

- Stimulated by fat and protein (lesser extent acid)
- Stimulates pancreatic enzyme secretion and potentiates secretin
- Stim growth of exocrine pancreas
- Regulates GB contraction
- Significant inhibition of gastric emptying
- Stim glucagon release

# GIP

- Discovered originally as inhibitor of gastric acid secretion, may not be physiologically significant in innervated stomach
- Stimulated by protein, fat, carbs
- Strong stim of insulin release
- Responsible for phenom of oral glucose load releases more insulin and is metab faster than equal amount IV
- Name changed from gastric inhibitory peptide to glucose dependent insulinotropic peptide

# Motilin

- Stimulated by nerves (lesser extent acid and fat)
- Stimulates the MMC
- Only known function
- Acid and fat in duodenum increase release
- Prevented by atropine and meal ingestion

# Protein

- In form of peptides and AA
- Stimulate gastrin and CCK

# Fat

- 8 or more C atoms or their monoglycerides
- Most potent stimulator of CCK
- Must be in absorbable form to trigger CCK
- Can stimulate secretin

# Carbs

- No alteration in release of gastrin, secretin, CCK
- Stimulates GIP

H<sup>+</sup>

- Stimulates secretin
- Hypersecretion can stim CCK
- Negative feedback on gastrin (pH <3.5 in antrum)
- If hyposecretion (atrophic gastritis, pernicious anemia) leads to high gastrin levels

# Antral Distention

- Stimulates gastrin
- Minor effect

# EtOH

- As wine (along with decaf coffee and calcium) stimulates gastrin
- Pure EtOH same concentration stimulates acid by not gastrin

# Insulin

- Secretion increased by secretin, gastrin, CCK, and GIP

# Increased Ca<sup>++</sup>

- Stimulates gastrin and CCK release

# Physiologic Role

- Unclear if any of above have important physiologic roles
- GIP leads to Insulin release and is important though
- May be important in disease states

# Candidate Hormones

- Enteroglucagon, Pancreatic polypeptide, peptide YY (tyrosine-tyrosine)
- May later fulfill all 4 criteria

# Pancreatic Polypeptide

- Inhibits both pancreatic bicarb and enzyme secretion (lowest dose requirement)
- Released by most meal constituents
- May act as modulator
- Difficult to prove its function since it inhibits pancreas but is made in pancreas

# Peptide YY

- Stimulated by meals, esp fat
- May appear in concentrations sufficient to inhibit gastric secretion and emptying = enterogastrone
- Effects not direct = does not inhibit secretin in response to gastrin or histamine
- Does inhibit neurally stimulated secretion
- Inh intestinal motility (? Enhance nutrient digestion/absorption)

# Enteroglucagons

- Same gene as glucagon
- Intestinal L cell makes GLP-1 that may have important physiologic actions
- Potent insulin releaser in absence of hyperglycemia
- Inh gastric secretion/emptying
- May mediate the ileal brake

# Neurocrines

- Peptides traced back to nerves of the gut
- Some are identical in brain and gut
- Substance P = stim intestinal motility and GB contraction
- Neurotensin = inc bld glc by stim glycogenolysis and glucagon release, inh insulin release
- 3 main ones: VIP, GRP(bombesin), Enkephalins

# VIP

- Exclusively in nerves
- Mediates smooth muscle relaxation in GI
- Mediates smooth muscle relax in bld vessels = vasodilation
- Effects through NO synthesis stimulation
- Can act like “relatives” secretin and GIP when inj into blood

# GRP (bombesin)

- Gastrin releasing peptide
- Nerves of gastric mucosa
- Released by vagal stim and mediates vagal release of gastrin
- Luminal protein digestion products may also stim gastrin via GRP

# Enkephalins

- In nerves in smooth muscle and mucosa
- Opiate receptors on circular smooth muscle cells mediated contraction
- Cause contraction of LES, pylorus, ileocecal sphincters
- May have intricate part in peristalsis
- Inh intestinal secretion and may slow transit

# Paracrines

- Interact with receptors close to point of release
- Diff to prove biologic significance
- Effects examined through specific blockers and in vitro perfused organs

# Somatostatin

- Inh gastrin release when the antral mucosa is acidified
- Directly inh gastric acid secretion
- Found in gastric and duodenal mucosa and pancreas
- Inh release of all gut hormones

# Histamine

- Produced in ECL cells from histidine
- Released by gastrin
- Stim acid secretion from parietal cells
- Potentiates the action of gastrin and Ach on acid secretion

# Gastrinomas

- Zollinger-Ellison Syndrome
- Small and diff to define/resect
- Mets grow slow
- High gastrin secretion -> hypersecretion of acid by trophic actions and stim of secretion
- Peptic ulcers, diarrhea, steatorrhea, hypokalemia due to lag acid amount in sm bowel

# VIPomas

- Causes pancreatic cholera due to release of VIP from pancreatic islet cell tumor
- Stim intestinal secretion of fluid and lytes -> copious diarrhea

# Tests

- Gastrin can be measured, lab dependent
- Overlap with gastrinoma and duodenal ulcer dz
- Can test it by protein meals, IV  $\text{Ca}^{++}$  infusion, secretin infusion
- Constant high gastrin means food stimulus not significant to raise gastrin level

# Ca<sup>++</sup> Infusion

- Inf 5mg/kg/hr Ca<sup>++</sup> gluconate for 3 hrs and measure acid secretion and collect blood for gastrin
- Peak gastrin 3 hrs after infusion
- If gastrinoma values double to over 500
- Duodenal ulcer dz may inc but usually not past 200-300

# Secretin Test

- Inj secretin
- Inhibits antral gastrin and stimulates tumor gastrin in almost all gastrinomas
- 1 U/kg given rapid IV inj
- Peak gastrin in 5-10 min
- If basal inc serum gastrin and acid hypersecretion and double gastrin in 5-10 min after secretin = strongly indicates gastrinoma