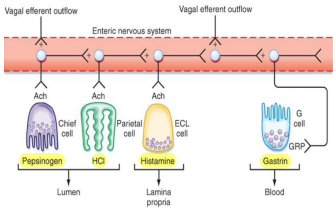
Physiology of gastric secretion :

- parietal cells secrete 2 liters of acid/day .
- for the function of the pepsin (digestive enzyme) the optimal PH is between (1.8- 3.5).
- stimulation of acid secretion involves H+/K+ -ATPase (proton pump) which uses ATP hydrolysis to pump H+ into the lumen in exchange for potassium ions .
- Chloride and hydrogen ions are secreted separately from the cytoplasm of parietal cells and mixed in the canaliculi .



Stimulants of acid secretion :

1- Ach from enteric neurons **.**
2- histamine from ECL(enterochromaffin-like) cells **.**
3- gastrin released by G cells **.**

Inhibitors of acid secretion :

1- somatostatin from D cells
* when gastric PH becomes less than 3 , gastric D cells release somatostatin to inhibit further secretion of . HCL in two ways :
a) direct effect on parietal cells .
b) inhibiting release of gastrin & histamine .

Gastric acid secretion phases :

1) cephalic phase
- smell ,sight , taste , thought of food -> activate enteric neurons .
- In humans, the major effect of gastrin is indirect through the release of histamine from ECL cells not through direct parietal cell stimulation.

2) Gastric phase
- Food stretch stomach walls -> activates neural reflex to stimulate acid secretion.
- Peptides & amino acids stimulate G cells to release gastrin.
- food acts as a buffer, raising the pH & thus removing the stimulus for somatostatin secretion.

3) Intestinal phase
- Once chyme enters the duodenum, it activates negative feedback mechanisms to reduce acid secretion.

Peptic ulcer :

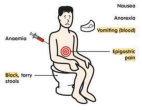
- defect in the lining of the stomach or duodenum .
- Causes :

1) H.pylori -most common-
2) Drugs (aspirin, NSAIDs)
3) Smoking
4) Stress
5) Alcohol
6) Gastrinomas - Gastrinomas are neuroendocrine tumors characterized by the secretion of gastrin with resultant excessive gastric acid production causing severe peptic ulcer disease and diarrhea, a combination referred to as the Zollinger-Ellison syndrome (ZES)-

*NOTE ZES is a rare gastrin-secreting tumors .

- Symptoms:

1) burning pain in stomach between meals or at night.
2) Bloating
3) Heartburn
4) Nausea
5) Vomiting.



In severe cases , symptoms include :

1) dark or black stool
2) Vomiting blood
3) Weight loss
4) Sever pain in the mid to upper abdomen.

- complications:
1)gastrointestinal bleeding (could be life threatening) .
2) cancer (H.pylori) .
3) perforation (hole in the wall).

- Treatment options :
1) Reduce acid secretion .
2) Neutralize acid in the lumen (antacids) .
3) Protect the mucosa from acid destruction .
4) Antibiotic to eradicate H.pylori —> so the ulcer should begin to heal on its own .

Drugs for peptic ulcer

Antacids	General info	Absorption	MOA	SE	Notes
Aluminum hydroxide	-drugs are over the counter (no prescription needed). -pts taking it complain about heartburn & dyspepsia (epigastric pain) -pain is usually associated with food -drug is given 1hr after a meal & works for 2hrs -general MOA → chemically neutralize HCl in the lumen. -ALL are contraindicated in pts with renal insufficiency (otherwise → cation accumulation)	Low → no systemic effects or metabolic alkalosis - but interferes with absorption of other drugs	-Reacts slowly in the lumen -No gas production Al(OH)3 +3HCl → AlCl3 + 3H2O	-constipation -interferes with other drugs absorption	Since Mg causes diarrhea & Al causes constipation → we can mix them in a single drug to overcome their side effects.
Magnesium hydroxide		Low → no systemic effects or metabolic alkalosis	-reacts slowly in the lumen -no gas production Mg(OH)2 + 2HCl → Mgcl2 +2 H2O	-diarrhea (laxative effect) → by increasing osmotic pressure in the lumen -acid rebound → after its effect is done ,acid increases too much (somehow it activates acid secretion)	
Calcium carbonate		Intermediate → can cause milk alkali syndrome	CaCO3 + 2 HCl → CaCl2 + **CO2** + H2O	-CO2 production → belching -acid rebound -milk alkali syndrome : -milk → hypercalcemia → can precipitate Resulting in stones -alkali → increased H2CO3 -elevation of serum phosphate ,urea ,nitrogen & creatinine	
Sodium bicarbonate		High → can cause hypertension	NaHCO3 + HCl → NaCl + H2O + CO2 -Short DOA	-CO2 → belching -acid rebound -may cause metabolic alkalosis -may raise blood pressure → Contraindicated in pts with hypertension	

H2 receptor antagonists	Clinical uses	MOA	Pharmacokinetics	SE
Cimetidine **Prototype**	**GERD** -given prophylactically before meals -heals erosive esophagitis in <50% -PPI are preferred (steadily control acid → no fluctuations) **Non – ulcer dyspepsia** **Stress –related gastritis (stomach sores)** -usually IV -can prevent bleeding **Peptic ulcers** -healing rate is > 80-90% after 6-8 weeks -not effective in case of H.pylori (you need antibiotic here) -not effective if NSAIDs is continued -replaced by PPI	**1.Decrease secretion of acid** -By selectively & competitively inhibiting the histamine receptor on parietal cells (thus, gastrin & Ach pathways) -can suppress both 1. 90% basal acid secretion (nocturnal) 2. 60% day time secretion (meal-stimulated) **2.Decrease pepsin concentration** -effect is dose dependent		-most side effects among all **CNS** -if given IV to elderly in ICU → Confusion & hallucinations **Endocrine** -inhibits estradiol (form of estrogen) metabolism : -female → increased prolactin -male → infertility (MAY) **Pregnancy & nursing mothers** -can cross placenta + appear in breast milk → contraindicated **Cardiovascular** -RARELY bradycardia & hypotension **Liver** -can inhibit CYP450 enzymes → increase t1/2 for many drugs metabolized by these enzymes → here we might need to change the dose of that drug -diarrhea, fatigue, constipation, myalgia in 3% of pts
Rantidine			-DOA → 12hrs	-CYP effect is 4-10 times less -diarrhea, fatigue, constipation, myalgia in 3% of pts
Famotidine			-50% metabolized by first pass metabolism → low bioavailability	-CYP effect is negligible -diarrhea, fatigue, constipation, myalgia in 3% of pts
Nizatidine			-little metabolism by first pass → higher bioavailability	

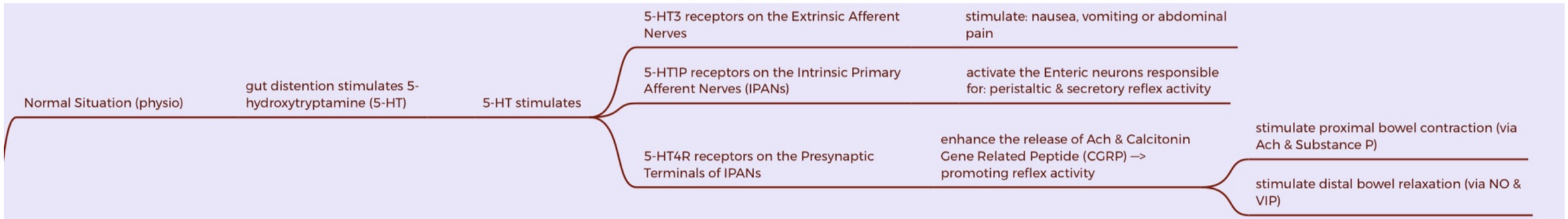
PPI	Pharmacokinetics	Pharmacodynamics (MOA)	Clinical uses	SE
Omeprazole (oral) Prototype **Rabeprazole (oral)** **Lansoprazole (oral & IV)** **Pantoprazole (oral & IV)** **Esmoprazole (oral & IV)**	-lipophilic weak bases -PPIs are prodrugs → activated by HCl in the parietal cell canaliculus → becomes protonated & 1000 folds concentrated -forms: -immediate release suspension -Immediate release capsule → both result in rapid response → they have short half lives, BUT, effect lasts for 24 hrs due to irreversiblr inhibition -should be given 1hr before meal	-activated drug binds covalently to H+/K+ ATPase (proton pump) → pump INHIBITION → 90-98% of HCl secretion is inhibited for 24% -can inhibit both basal & meal stimulated secretions	Efficacious & safe drugs **GERD** -drugs of choice **Non ulcer dysplasia** -modest activity -only 10-20% more beneficial than placebo **Stress related gastritis** -given nasogastric (usually oral immediate release omeprazole) -if nasogastric tube isn't suitable → IV H2 antagonists are preferred **Gastrenoma & other hypergastrenemia conditions** -usually high doses of omeprazole **Peptic ulcer** -healing rate = 90% -used for 4-6 weeks -H.pylori ulcers : -PPI have synergetic effect with antibiotics → By lowering their MIC -TRIPLE therapy → PPI BD + clarithromycin 500mg BD + Amoxicillin 1mg BD or metro 500mg BD -NDAID associated ulcer: -PPI promotes ulcer healing despite continued use of NSAID -can be used porphilactically -rebleeding peptic ulcer: -high Ph may enhance coagulation → preventing rebleeding -oral or IV	**B12 deficiency** -reduction of IF → less cyanocobalamine (B12) absorption → increased risk of GI & pulmonary infections -note: B12 can help balance immune responses to better fight infections **Cancers** -chronic inflammation in gastric body → atrophic gastritis → intestinal metaplasia -hypergastrinemia → hyperplasia of ECL cells → carcinoids (confirmed in rats) + increase proliferative rate of colonic mucosa **Drug interactions** -affects the absorption of some drugs due to decreased gastric acidity → EX. Digoxin & ketoconazole -omeprazole can inhibit the metabolism of drugs such as Diazepam & phenytoin (depression & epileptic drugs) -Rabeprazole & pantoprazole have no significant interaction **Pregnancy** Not teratogenic in animals , but not preferably used in pregnancy. **DIARRHEA** -headache -abdominal pain

Laxatives

Treatment	What are they?	Types	MOA	SE
Non pharmacologic remedies		-high fiber diet → lubrication -adequate fluid intake -respond to nature call → less solid feces -regular exercise (walk) → move abdominal muscles		
Bulk forming laxatives	-indigestible , hydrophilic colloids	**Natural plant products** -psyllium -sterculia (normacol) -methylcellulose **Synthetic fibers** -polycarbophil	They absorb water → forming a bulk in the colon (emollient gel) → distension of the colon → peristaltic reflex	-bloating -flatus
Stool surfactants (softners)	-oral or rectal substances that allow water & lipids to penetrate & lubricate the stool	-Docusate -glycerin suppository -mineral oil (oral)	**Mineral oil** -surrounds the fecal matter lubricating it + preventing water absorption from the core	**Mineral oil** -aspiration can cause LIPID PNEUMONIA -can impair absorption of fat soluble vitamins
Osmotic laxatives (purgatives)	-soluble (osmotic) -non- absorbable	-Magnesium oxide (milk of magnesia) -sorbitol -lactulose -polyethylene glycol (PEG)	-osmotically move water into the lumen → increase stool liquidity **Magnesium oxide (milk of magnesia)** -large doses of magnesium citrate & sodium phosphate = purgation تطهير + rapid bowel evacuation within 1-3 hrs → volume depletion -used before X ray images **PEG** -inert , non-absorbable & osmotically active sugar -taken with sodium sulfate, chloride, bicarbonate & potassium chloride -safe solution → - no intravascular fluid or electrolyte shifts (BALANCED) -no flatus or cramps -use → -complete colonic cleaning before endoscopy … should be ingested rapidly (4L over 2-4 hrs) -chronic constipation … powder is mixed with water or juice	**Lactulose** Severe flatus & cramps
Stimulant laxatives (chathartics)		-anthraquinone derivatives (aloe, senna, cascara) -castor oil (زيت الخروع) -Tegaserod	-directly stimulate the ENS → colonic electrolyte & fluid secretion **Use** -neurological impaired patients & in bed bound pts in long term care facilities	-can lead to dependence & destruction of the myenteric plexus → colonic atony (weakness) & dilation (pts cant defecate unless they take the drug)

Stimulant laxatives

Drug	Pharmacokinetics	MOA	SE	Clinical uses
Anthraquinone derivatives	-poorly absorbed	-after hydrolysis → produces bowel movement in (6-12 hrs) -not carcinogenic	-brown pigmentation in the colon (melanosis coli)	
Caster oil		-hydrolyzed in the upper intestine into Ricinoleic Acid → local irritant -was used to clean the colon before procedures		
Tegaserod		-it's a serotonin 5-HT4 partial agonist → 1.enhances the release of NT that promote gastric, small & large intestine emptying (but has no effect on esophagus motility) 2.stimulates cAMP – dependent Cl secretion → increasing stool liquidity	-very safe drug كان زمان ... هلأ انسحب -diarrhea occurs in 9% of pts ,but resolves within days -expensive ممكن يقل Systemic parasympathetic Stimulation	-CIC (chronic idiopathic constipation) -IBS (irritable bowel syndrome) -gastroparesis (delayed gastric emptying) -non ulcer dyspepsia يعتبر آخر خيار



cases of contra-indication :-

1. undiagnosed abdominal pain → could be appendicitis
2. obstruction

} giving laxative may cause perforation & peritonitis