DRUGS ACTING ON GASTROINTESTINAL TRACT

Major function of GIT include;

- **Digestion and absorption of food,**

- **In addition ,its endocrine system and neural network has an integrative role**

- **Major GIT disorders include PUD, constipation, nausea and vomiting, etc…**

- **Medicines for treating these gastrointestinal disorders comprise some 8% of all prescriptions**

Drugs used for constipation;

LAXATIVES

- Used in the treatment of constipation, poison removal, preparation of bowel for surgery and for removal of parasites after anthelementics
- Classified by their major mechanism of action

1. BULK FORMING LAXATIVES
   - Indigestible, hydrophilic Colloids that absorb water, forming a bulky, emollient gel that distends colon & promotes peristalsis.
   - Natural: psylium, methylcellulose
   - Synthetic fiber: polycarbophil
   - Bacterial digestion of the fiber in colon ⟶ bloating and flatus

GIT cont'd

2. STOOL SOFTNERS/SURFACTANT AGENTS

- Change surface tension of fluids in the bowel - this has an emulsifying effect on feces, making them retain more water and hence softer - easier to pass out
- Glycerine suppositories.
- Docusate oral or enema
- Liquid paraffin
  - Oily, liquid substance
  - Not used anymore
- Absorbs the fat soluble vitamins in the gut, and therefore you loose your fat soluble vitamins

GIT cont'd

3. OSMOTIC LAXATIVES

- Soluble but not absorbable, resulting in increased stool liquidity

- treatment/prevention of acute/chronic constipation, respectively

- **Nonabsorbable sugar**: sorbitol & lactulose
  - ♦ metabolized by colonic bacteria → severe flatus & cramp
- **Nonabsorbable salt**: magnesium oxide/ milk of magnesia
  - ♦ hypermagnesemia in renal insufficient patient if used for prolonged period

- High dose of osmotically active agents produce purgation within 1-3hs

- Balanced polyethylene glycol: lavage solution containing PEG are used for complete colonic cleansing prior to GI endoscopy

GIT cont'd

4. STIMULANT LAXATIVES/ CATHARTICS

- Direct stimulation of the enteric nervous system and colonic fluid and electrolyte secretion
- Long term: dependency & destruction of myenteric plexus; atony
- Useful in neurologically impaired and in bed bound patients in long term care facility
- Anthraquinone derivatives
  -Aloe, senna & cascara: bowel movement in 6-8hs after p.o.
  - cause brown pigmentation of colon "melanosis coli"
- Caster oil: hydrolysed in small intestine to ricinoleic acid-irritant that stimulates motility.

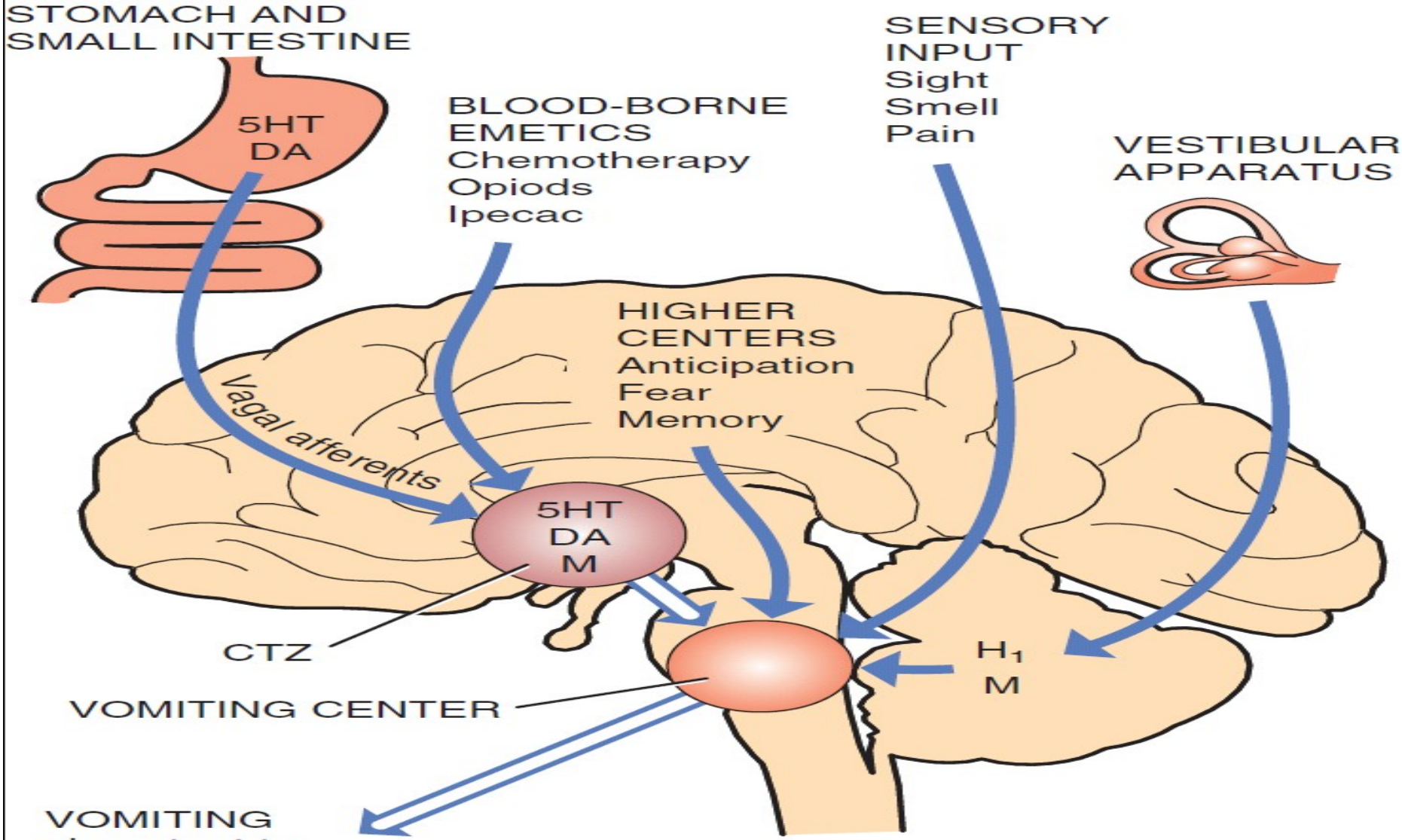
GIT cont'd

TREATMENT OF DIARRHOEAS

- Therapeutic measures:
  - treatment of fluid depletion, shock, and acidosis
  - maintenance of nutrition
  - drug therapy
- Rehydration
  - Intravenous rehydration in severe fluid loss [10% body weight]
  - Oral rehydration if the fluid loss is mild
- Antimicrobials are of no use in diarrhea due to noninfective causes
- Antimicrobials are useful only in severe disease
- Travellers diarrhea:mostly due to C.pylori, virus [cotrimoxazole, norfloxacin, doxycycline, erythromycin]

ANTI EMETICS

- Main area responsible for vomiting is the vomiting center
- It receives input from many areas:
  - Chemoreceptor trigger zone -picks up circulating chemical in the blood
  - Vestibular apparatus
  - vagal afferents from the gut
  - Direct input from gut (reflex)
- Receptors involved in the emetic response
  - On the CTZ: 5HT3, D2
  - On the vagal afferents: 5HT3
  - In the vomiting center: Muscarinic, H1 receptors



Receptors

5HT = Serotonin
DA = Dopamine
M = Muscarinic cholinergic
H_1 = Histamine$_1$

GIT cont'd

- Drugs which causes nausea and vomiting
  - Apomorphine (and Bromocriptine)
    - Acts on the D2 receptor in the CTZ to cause vomiting
  - Cisplatin
    - causes release of serotonin in the gut

GIT cont'd

ANTI EMETIC DRUGS CHOICE

1. Motion Sickness

❖ **Promethazine**

- H1 antagonist, antimuscarinic actions
- Used as a sedative in children
- Effective at preventing motion sickness (since the vestibular afferents input in the vomiting center which has H1 and Muscarinic receptors
- Not used for the driver [drowsy]

Hyoscine (scopolamine)-**anti-cholinergic.**

- Available as oral, subcutaneous, and transdermal
- Can be used as a patch behind the ear
- suppresses nerve traffic in neuronal pathway from vestibular apparatus of inner ear to vomiting center
- common side effects are dry mouth, blurred vision, drowsiness
- more severe side effects include urinary retention, constipation, and disorientation

GIT cont'd

2. CTZ Mediated Vomiting

- Prochlorperazine
  - phenothiazine, D2 antagonist
  - Has no antipsychotic effects
  - Useful as an antiemetic as well as for dizziness
  - Has minor anticholinergic effects (it may work in motion sickness, however, the above drugs are preferred)
  - blocks D2 receptors elsewhere (e.g. substantia nigra) cause extrapyramidal effects
  - Chlorpromazine can also be used as an antiemetic, although it tends to be very sedative

GIT cont'd

- Metoclopromide
  - D2 antagonist, weak 5HT3 antagonist
  - Increases motility of the gut in the upper regions
  - Useful because when someone is nauseous, there is often gastric stasis
  - helps absorption of drugs as it stimulates gastric emptying

GIT cont'd

3. Vomiting associated with vagal afferents (gut disorders, heart, gut irritants - all stimulate the 5HT3 receptor on the vagal afferents)

- Ondansetron
  - Most effective drug available for suppressing nausea and vomiting caused by cisplatin and other highly emetogenic anticancer drugs.
  - $5HT_3$ antagonist
  - Effective in patients receiving cancer chemotherapy (radiation or cisplatin – stimulate the release of serotonin in the gut)
  - Can also be used for CTZ nausea

DRUGS FOR PEPTIC ULCER

- Ulcer: Breakdown of the protective mucosal layer
  - Common sites: Duodenum & Stomach
  - Pain is due to:
    - Acid acting on the erosion
    - Increase in the motility of the gut, causing increased intramural tension (antimotility agents decrease the pain)

Causes of peptic ulcer

- Imbalance b/n protective and aggressive factors
- Defensive factors; mucus, bicarbonate, sub mucosal blood flow and prostaglandins.
- Aggressive factors;

✓ ***H. pylori***

✓ ***Excess HCL or pepsin secretion***

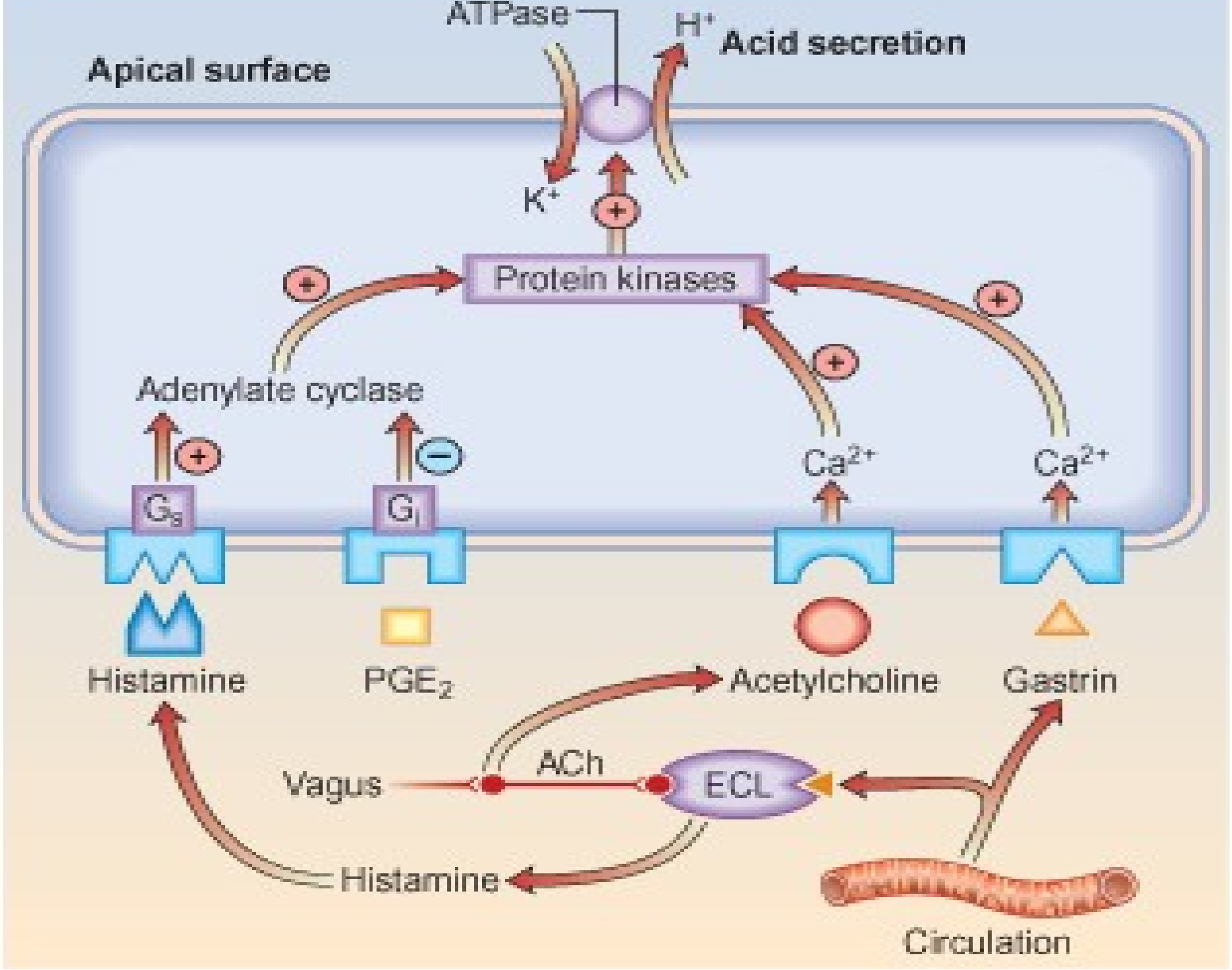
✓ **Stress**

✓ **NSAIDs**

✓ **Alcohol, smoking, spicy foods etc**

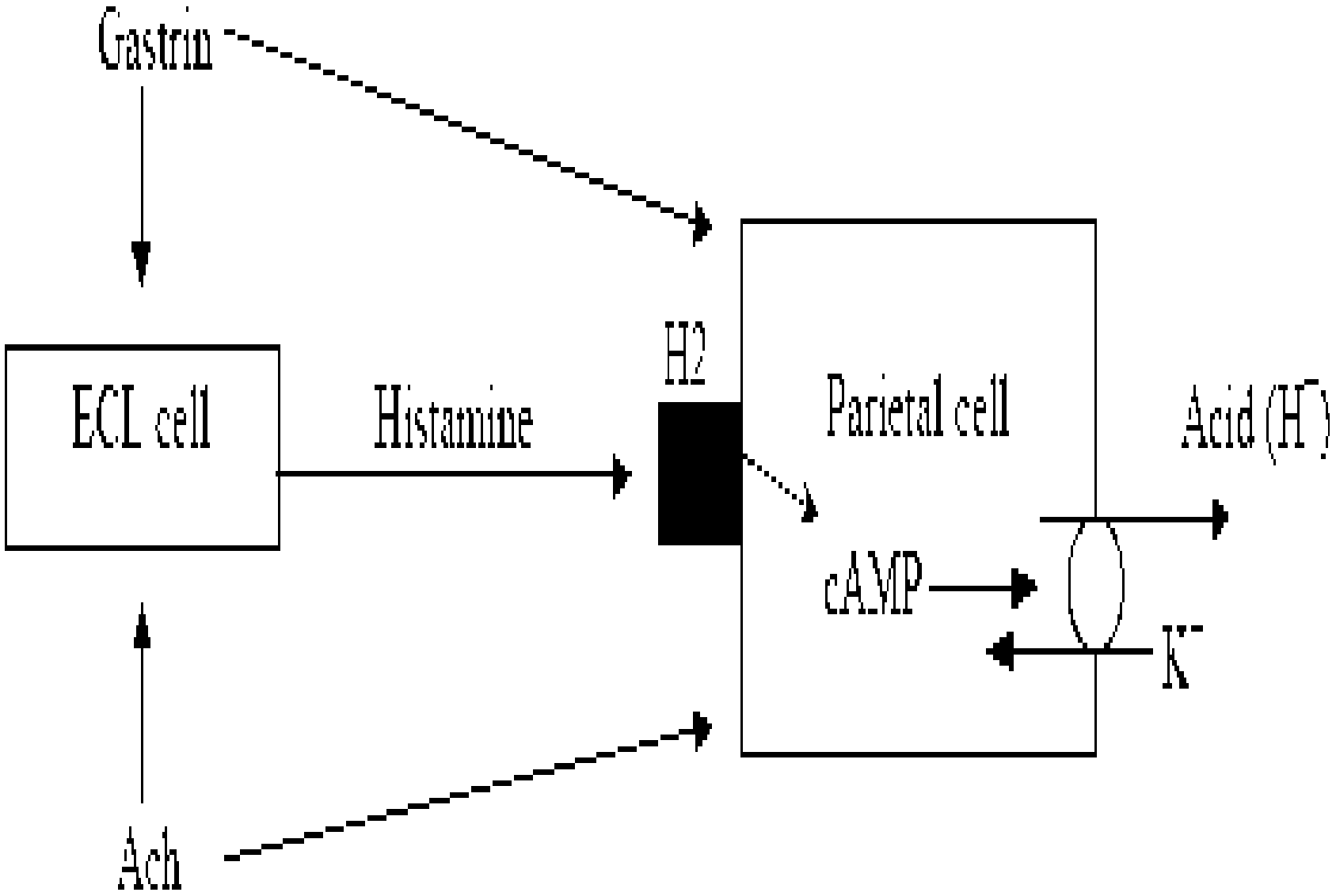
Treatment strategy;

✓ decrease aggressive factors or increase defensive factors



lsevier. Kumar & Clark: Clinical Medicine 6e - www.studentconsult.com

Mechanisms of HCL secretion and Major Drug targets for PUD


Gastrin
ECL cell
Histamine
H2
Parietal cell
Acid (H+)
cAMP
K+
Ach

Antacids

- Weak bases that neutralize acid
- Also inhibit formation of pepsin (As pepsinogen converted to pepsin at acidic pH)
- Present day antacids :
  - Aluminium Hydroxide
  - Magnesium Hydroxide
- OTC drug for symptomatic relief of dyspepsia

Duration of action :

- 30 min when taken in empty stomach
- 2 hrs when taken after a meal
- Side effects :

Al^{3+} antacids – constipation (As they relax gastric smooth muscle & delay gastric emptying)

Mg^{2+} antacids – Osmotic diarrhoea .

In renal failure Al^{3+} antacid – Aluminium toxicity & Encephalopathy

Drug interaction of antacids;

- Adsorb drugs and form insoluble complexes that are not absorbed .

Clinical importance :

- Interactions can be avoided by taking antacids 2 hrs before or after ingestion of other drugs .
- rational to combine aluminium hydroxide and magnesium hydroxide in antacid preparations
  - ✓ Combination provides a relatively fast and sustained neutralising capacity .

    (Magnesium Hydroxide – Rapidly acting

    Aluminium Hydroxide - Slowly acting)
  - ✓ Combination preserves normal bowel function.

    (Aluminium Hydroxide – constipation

    Magnesium hydroxide – diarrhoea)

Histamine H_2 Receptor Antagonist

- Reversible competitive inhibitors of H_2 receptor
- Highly selective, No action on H_1 or H_3 receptors
- Very effective in inhibiting nocturnal acid secretion (as it depends largely on Histamine)
- Modest impact on meal stimulated acid secretion (As it depends on gastrin, acetyl choline and histamine)

comparison of the different H2 receptor antagonists

	Cimetidine	Ranitidine	Famotidine	Nizatidine
Bioavailability	80	50	40	>90
Relative Potency	1	5 -10	32	5 -10
Half life (hrs)	1.5 - 2.3	1.6 - 2.4	2.5 - 4	1.1 -1.6
Duration (hrs)	6	8	12	8
Inhibition of CYP 450	1	0.1	0	0
Dose mg(bd)	400	150	20	150

H_2 Blockers–Side effects & Interactions

- Extremely safe drugs
- Cimetidine inhibits CYP450 & increases conc. of Warfarin, Theophylline, Phenytoin, Ethanol
- CNS- Mental status change (confusion, agitation, hallucination) in i.v. H2 antagonist
- Endocrine effect: cimetidine inhibits binding of dihydrotestosterone, inhibits metabolism of estradiol, increase prolactin [gynecomasia, impotence in male; galactorrhea]
- Cross the placenta &secreted into breast milk

Drug interaction:

- cimetidine interfere hepatic cytochrome P450 drug metabolism pathways
- ✓ warfarin,
- ✓ theophylline,
- ✓ phenytoin, lidocaine, quinidine, propranolol, TCAs,
- ✓ several benzodiazepines,
- ✓ CCBs, sulfonylureas, metronidazole, and ethanol

Proton Pump Inhibitors (PPIs)

- Most effective drugs in antiulcer therapy
- Irreversible inhibitor of $H^+ K^+$ ATPase
- Prodrugs requiring activation in acid environment
- Weakly basic drugs & so accumulate in canaliculi of parietal cell
- Activated in canaliculi & binds covalently to extracellular domain of $H^+ K^+$ ATPase
- Acid secretion resumes only after synthesis of new molecules
- Since they require acid for activation - given 1 hr before meals
- Other acid suppressing agents not coadministered

Examples of PPIs and their doses;

Omeprazole	20 mg o.d.
Esomeprazole	20 - 40 mg o.d.
Lansoprazole	30 mg o.d.
Pantoprazole	40 mg o.d.
Rabeprazole	20 mg o.d.

PPI Side Effects;

- Extremely safe drugs
- Inhibit CYP 450 & hence metabolsim of warfarin, phenytoin, etc
- Pantoprazole & Rabeprazole have no significant interactions

Mucosal Protective Agents

Sucralfate

Misoprostol

Colloidal Bismuth compounds

Sucralfate;

- Salt of sucrose complexed to sulfated aluminium hydroxide
- In acidic pH polymerises to viscous gel that adheres to ulcer crater
- Taken on empty stomach 1 hr. before meals
- Concurrent antacids, H_2 antagonist avoided

(as it needs acid for activation)

Misoprostol;

- PGE_2 analogue
- Modest acid inhibition
- Stimulate mucus & bicarbonate secretion
- Enhance mucusal blood flow
- Approved for prevention of NSAID induced ulcer
- Diarrhoea & cramping abd. pain – 20 %
- Not so popular as P.P.I are more effective & better tolerated

PGE**2** protects the stomach in a number of ways:

- ✓ limits the amount of gastric acid being released
- ✓ It increases mucous secretion
- ✓ It increases blood flow to the stomach

- Side effects:
- Colic and diarrhoea
- Dangerous in pregnancy ⟵ PGE**2** contracts the uterus

Colloidal Bismuth Compounds

- Coats ulcer, stimulates mucus & bicarbonate secretion
- Direct antimicrobial activity against H.pylori
- May cause blackening of stools & tongue
- Not used for long periods – bismuth toxicity

Available compounds :

- Bismuth subsalicylate – in USA
- Bismuth sobcitrate – in Europe
- Bismuth dinitrate

TREATMENT OF PUD CAUSED by H PYLORI

- *H pylori is a gram negative bacilli that colonize itself in acidic environment of stomach.*
- Now generally considered to be a major cause of chronic gastritis.
- Eradication of *H. pylori* infection promotes rapid & long-term healing of ulcers.
- If a patient with PUD is positive for H Pylori, then it can be eradicated with a 1- or 2-week regimen of 'triple therapy'.
- Triple theraoy comprises a PPI in combination with antibiotics **amoxicillin** or **metronidazole** and **clarithromycin**.
- In case of the 2-week regimen, bismuth-containing preparations are added.

Regimens Recommended for Eradication of *H. pylori* Infection

Drug	Dose
TRIPLE THERAPY	
1. Bismuth subsalicylate *plus*	2 tablets qid
Metronidazole *plus*	250 mg qid
Tetracycline[a]	500 mg qid
2. Ranitidine bismuth citrate *plus*	400 mg bid
Tetracycline *plus*	500 mg bid
Clarithromycin *or* metronidazole	500 mg bid
3. Omeprazole (lansoprazole) *plus*	20 mg bid (30 mg bid)
Clarithromycin *plus*	250 or 500 mg bid
Metronidazole[b] *or*	500 mg bid
Amoxicillin[c]	1 g bid
QUADRUPLE THERAPY	
Omeprazole (lansoprazole)	20 mg (30 mg) daily
Bismuth subsalicylate	2 tablets qid
Metronidazole	250 mg qid
Tetracycline	500 mg qid

Summary of drugs for PUD

1. PUD only

First Line

Ranitidine, 150 mg P.O. BID OR 300 mg at bedtime for 4 – 6 weeks.

Alternatives

Cimetidine, 400 mg P.O. BID, with breakfast and at night, OR 800 mg at night for 4 - 6 weeks.

OR

Famotidine, 40 mg, P.O. at night for 4 – 6 weeks.

OR

Omeprazole, 20 mg P.O. QD for 4 weeks (DU) or 8 weeks.

2. PUD associated with H. pylori

First Line

Amoxicillin, 1g, P.O. BID

PLUS

Clarithromycin, 500mg P.O. BID

PLUS

Omeprazole, 20mg P.O. BID (OR 40mg QD), all for 7 - 14 days.

Alternative

Clarithromycin, 500mg P.O. BID

PLUS

Metronidazole, 500mg, P.O. BID

PLUS

Omeprazole, 20mg P.O. BID OR 40mg QD for 7 - 14 days .