# BHARATHIDASAN UNIVERSITY

Tiruchirappalli- 620024, Tamil Nadu,
India

## Programme: M.Sc., Biomedical Science

**Course Title : Pharmacology and Toxicology**
**Course Code : BM35C7**

## Unit-III
## Pharmacology of GIT- Part 2

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# Peptic ulcer

- Occurs g.i.t. which is exposed to gastric acid and pepsin, i.e. the stomach and duodenum.
- Imbalance between the aggressive (acid, pepsin, bile and H. pylori) and the defensive (gastric mucus and bicarbonate secretion, prostaglandins, nitric oxide, innate resistance of the mucosal cells ) factors

- Gastric juice - hydrochloric acid, pepsin, rennin (in children), neutral chlorides, mucus, intrinsic factor and traces of potassium, ammonium and calcium
- The gastric acid and pepsin are secreted by the main gastric glands, containing highly specialised cells, present all over the body and fundus of the stomach.

The rate and the composition of the secretion of main gastric glands

- number of acid-secreting cells
- emotional factors,
- digestive state,
- hormonal status
- Presence of extrinsic chemical stimuli such as caffeine and histamine.

- The parietal (oxyntic) cells are located in the walls of the midsection of the oxyntic glands, the secretory unit of the gastric mucosa.
- The parietal cell has prominent cytoplasmic tubulo-vesicles.
- In addition, oxyntic glands contain chief, mucous, enterochromafin like (ECL) cells and somatostatin cells

- A variety of psychosomatic, humoral and vascular derangements have been implicated and the importance of Helicobacter pylori infection as a contributor to ulcer formation and recurrence has been recognized.

- In gastric ulcer, generally acid secretion is normal or low.
- In duodenal ulcer, acid secretion is high in half of the patients but normal in the rest.

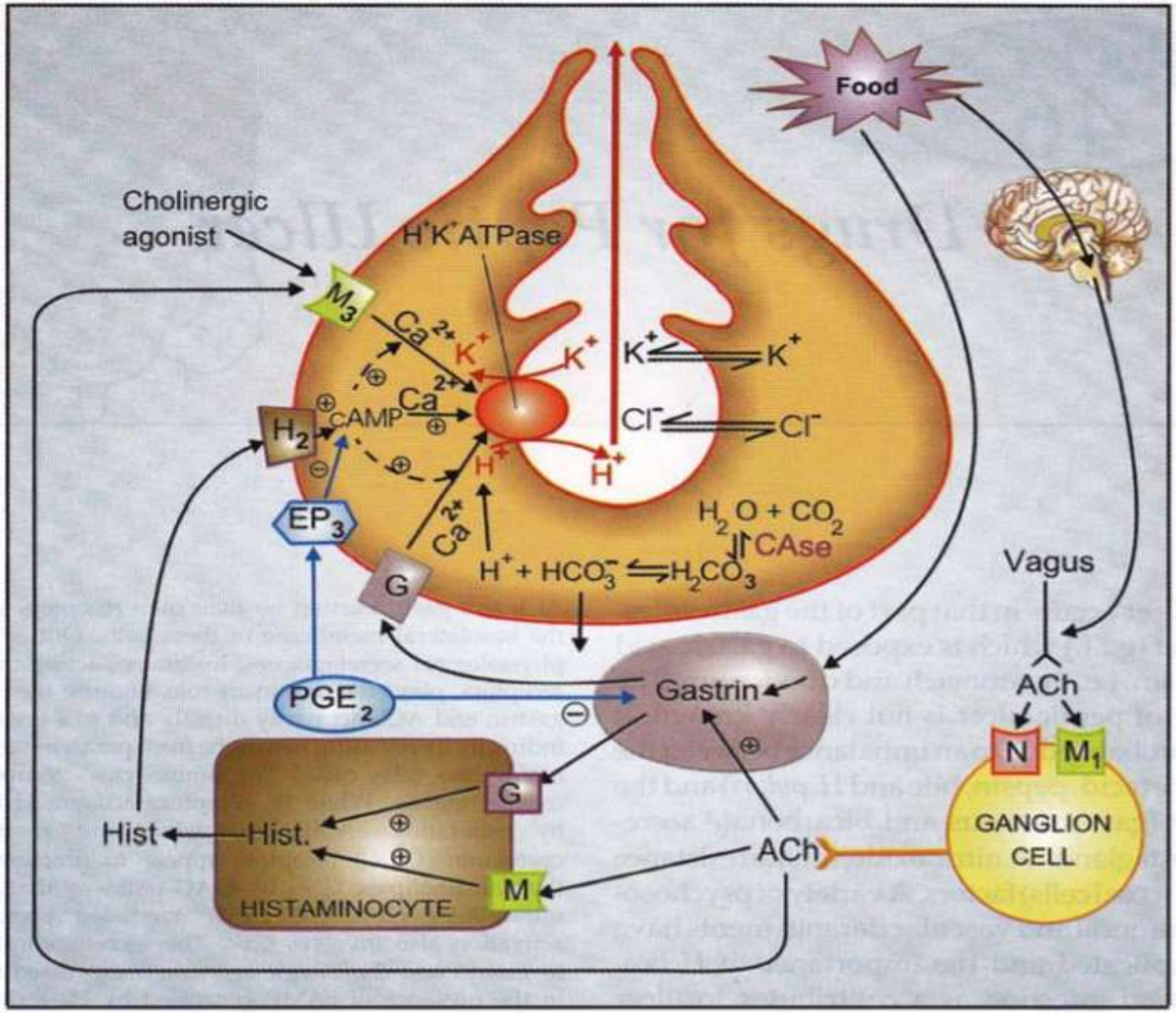



**Fig. 46.1:** Secretion of HCl by gastric parietal cell and its regulation
CAse.—Carbonic anhydrase; Hist.—Histamine; ACh.—Acetylcholine; G—Gastrin/cholecystokinin($CCK_2$) receptor; M.—Muscarinic receptor; N—Nicotinic receptor; $H_2$—Histamine $H_2$ receptor; $EP_3$—Prostaglandin receptor; + Stimulation; –Inhibition.

# Reduction of gastric acid secretion

$H_2$ antihistamines:

Cimetidine, Ranitidine, Famotidine, Roxatidine

Proton pump inhibitors:

Omeprazole, Lansoprazole, Pantoprazole, Rabeprazole, Esomeprazole

Anticholinergics:

Pirenzepine, Proparitheline, Oxyphenonium

Prostaglandin analogue: Misoprostol

# Neutralization of gastric acid (Antacids)

Systemic:

Sodium bicarbonate, Sod. citrate

Nonsystemic:

Magnesium hydroxide, Mag. trisilicate, Aluminium hydroxide

Ulcer protectives:

Sucralfate, Colloidal bismuth sub citrate (CBS)

Anti-H. pylori drugs:

Amoxicillin, Clarithromycin, Metronidazole, Tinidazole, Tetracycline

# $H_2$ Antihistamines

- These drugs act selectively by competitive blockade of parietal cell H2 receptors.
- However, they can cause tolerance probably due to down regulation of receptors.
- A rebound increase in acid secretion may occur after their withdrawal.

# CIMETIDINE

- Inhibits markedly **(80-90%) histamine, pentagastrin, caffeine and vagus (ACh)** stimulated gastric acid secretion.
- It also inhibits the **basal and meal**-stimulated gastric secretion.
- Given orally, it reduces the acid secretion to about **20% within an hour.**
- The effect is on both **volume and acid content** of the gastric juice; the **pepsin** secretion is **less affected.**

# Absorption, fate and excretion:

- (60-80%) oral Absorption
- Bioavailability is **reduced to ⅓rd** given with sucralfate or large doses of antacids
- Therapeutic effect - single dose lasts for **5-8 hours.**
- Excreted unchanged in the urine within **24 hours.**
- It can cross the **placenta and is secreted in milk.**
- ADR- Rashes, diarrhoea, muscle pain, fatigue and bradycardia.
- Blockade of **cerebral H2-receptors** can cause drowsiness, mental confusion, delirium and hallucinations in the elderly and in those with hepatic or renal failure.

- Cimetidine inhibits several cytochrome P-450 isoenzymes and reduces hepatic blood flow.
- It inhibits the metabolism of many drugs so that they can accumulate to toxic levels, e.g. theophylline, phenytoin, carbamazepine, phenobarbitone, sulfonylureas, metronidazole, warfarin
- Dose: For ulcer healing **400 mg BD** or **800 mg at bed time orally**; maintenance 400 mg at bed time; for **stress ulcer 50 mg/hr** i.v. infusion.

- Duodenal ulcer
- Gastric ulcer
- Stress ulcers and gastritis
- Zollinger-Ellison syndrome
- Gastroesophageal reflux disease (GERD)
- Prophylaxis of aspiration pneumonia

# Mechanism of action: PPI

- After absorption from the intestine, PPI diffuse from the blood into the parietal cells, are secreted into and get ionised at the acid pH and inactivate the enzyme H+-K+-ATPase irreversibly.
- This causes marked inhibition of gastric acid secretion.
- They have **negligible effect on pepsin content**.
- There is **less rebound** increase in acidity

# Overview

## Physiology of acid secretion

Parietal cells are located in the body of the stomach and secrete hydrochloric acid (HCl) into the lumen.

- Water and $CO_2$ are combined to produce hydrogen ($H^+$) ions and $HCO_3$ ions by the action of the carbonic anhydrase enzyme.
- $H^+$ is transported to the lumen of the stomach via the $H^+/K^+$ ATPase pump.
- $HCO_3$ is exchanged for chloride ($Cl^-$) ion.
- $H^+$ and $Cl^-$ combine to form the final product: HCl

Ion transport in parietal cells:

Carbonic acid disassociates into a hydrogen ($H^+$) ion and bicarbonate ($HCO_3^-$). The $H^+$ is exchanged for potassium ($K^+$) in the apical membrane by the $H^+/K^+$ ATPase.

Bicarbonate is exchanged for chloride ($Cl^-$) in the basolateral membrane, which then moves into the lumen.

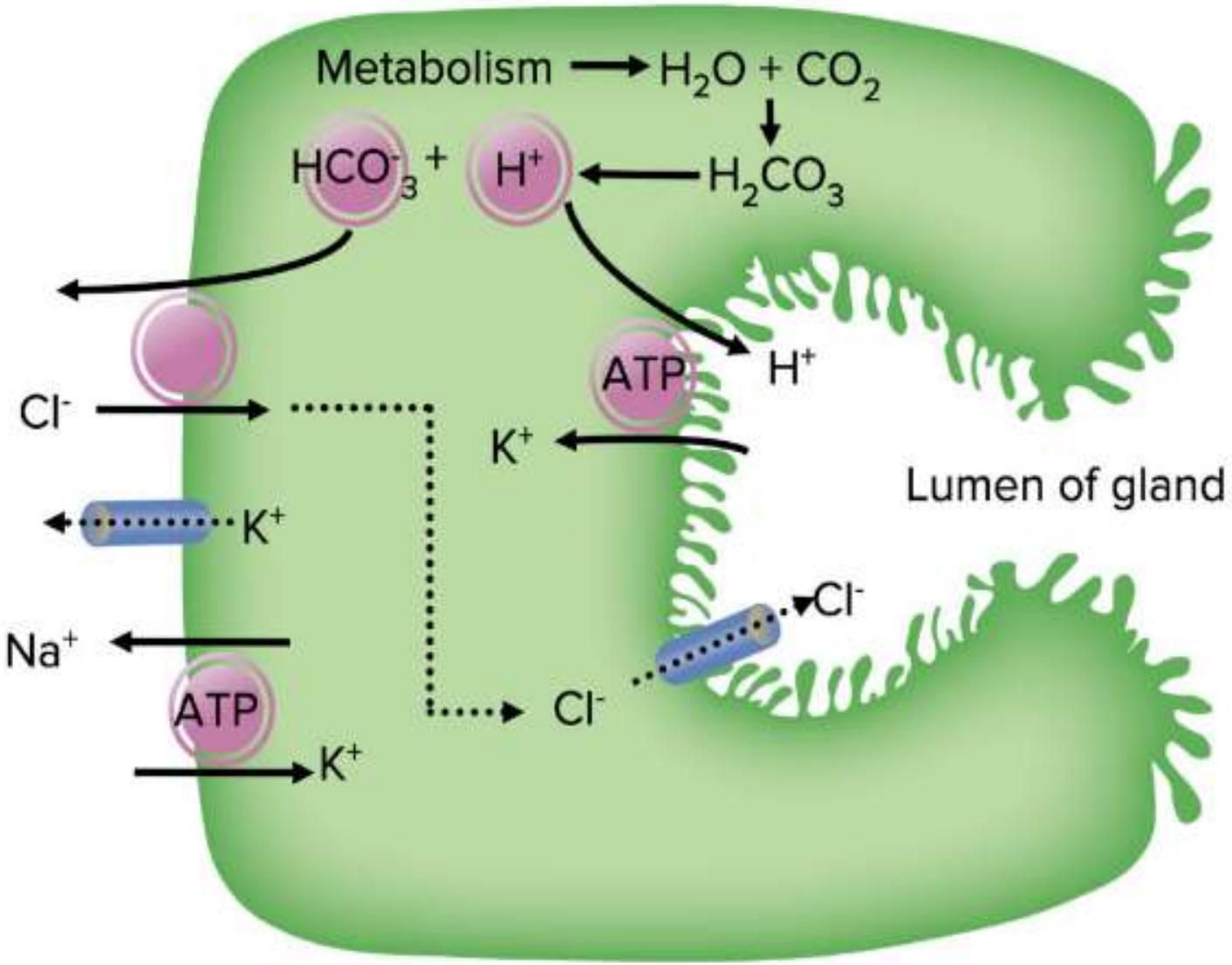
The $Na^+/K^+$ ATPase pump in the basolateral membrane creates the cell's electrochemical gradient.

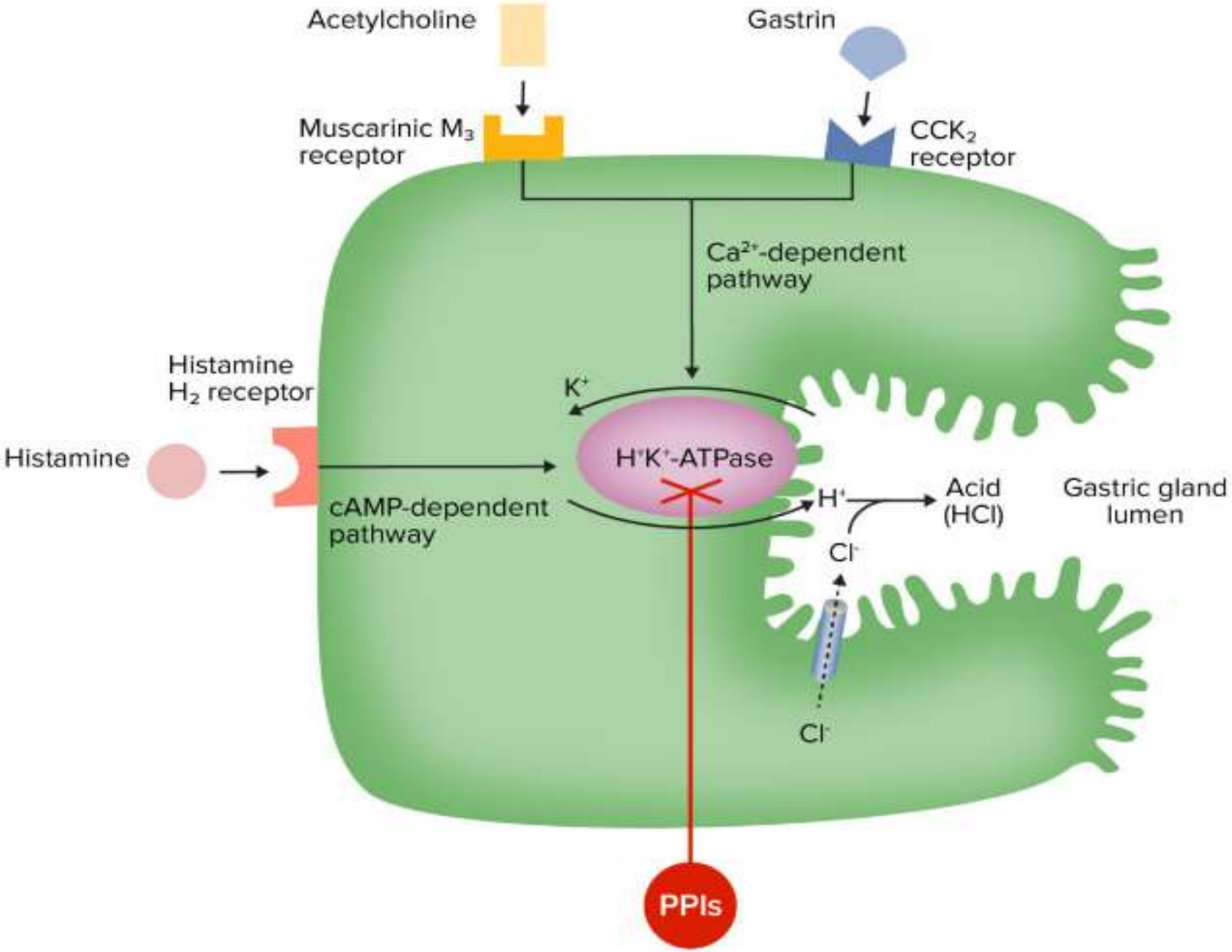
# Mechanism of action

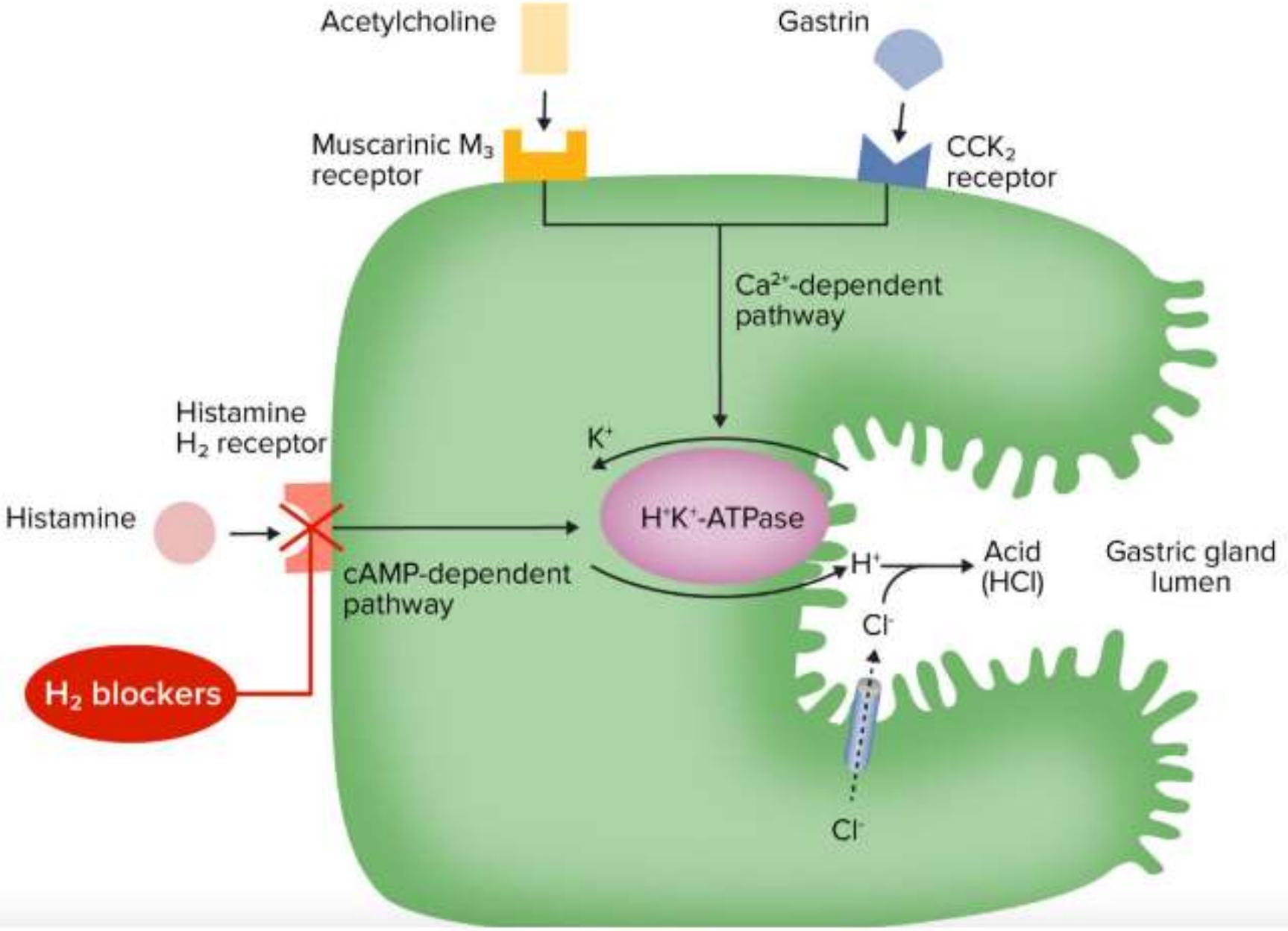
- Administered as a prodrug → concentrated in secretory canaliculi of the parietal cell
- Converted to an active form (a sulfonamide cation) → covalently binds to the $H^+/K^+$ ATPase pump
- Causes irreversible inhibition → prevents movement of $H^+$ into the gastric lumen → ↓ acid secretion
- Inhibits both basal acid output and meal-stimulated output

Mechanism of action of proton pump inhibitors (PPIs):

The drugs accumulate in the gland lumen, convert to the active form, and covalently bond to the $H^+/K^+$ ATPase, which results in irreversible pump inactivation and reduced acid secretion.


Metabolism
$H_2O + CO_2$
$HCO_3^-$ +
$H^+$
$H_2CO_3$
$H^+$
ATP
$Cl^-$
$K^+$
Lumen of gland
$K^+$
$Cl^-$
$Na^+$
ATP
$Cl^-$
$K^+$


Acetylcholine
Gastrin
Muscarinic $M_3$ receptor
$CCK_2$ receptor
$Ca^{2+}$-dependent pathway
Histamine $H_2$ receptor
Histamine
$K^+$
$H^+K^+$-ATPase
cAMP-dependent pathway
$H^+$
Acid (HCl)
Gastric gland lumen
$Cl^-$
$Cl^-$
PPIs


Acetylcholine
Gastrin
Muscarinic $M_3$ receptor
$CCK_2$ receptor
$Ca^{2+}$-dependent pathway
Histamine $H_2$ receptor
$K^+$
Histamine
$H^+K^+$-ATPase
cAMP-dependent pathway
$H^+$
Acid (HCl)
Gastric gland lumen
$Cl^-$
$H_2$ blockers
$Cl^-$

- All of them have short plasma t½, 0.5-2 hours but the action lasts much longer.
- All PPIs are acid labile and the tablet should be swallowed unbroken/uncrushed;
- Drug should be given as enteric coated granules

# OMEPRAZOLE

- This is a substituted **benzimidazole** with potent and prolonged action.
- As the concentration of the proton pump molecules in the parietal cells is highest after a prolonged fast at night, the PPIs act best when taken about **½ hour before the breakfast.**
- Dose dependent suppression of gastric acid secretion; **without anticholinergic or $H_2$ blocking action.**

- **Oral absorption -50%,** - instability at acidic pH.
- Bioavailability of all **PPIs is reduced by food;** they should be taken in empty stomach, followed 1 hour later by a meal to activate the H+K+ ATPase
- Plasma protein bound, rapidly metabolised in liver by **CYP2C19 and CYP3A4**
- Metabolites are **excreted in urine.**
- **Tight binding to its target enzyme** -it can be detected in the gastric mucosa long after its disappearance from plasma.

# Prostaglandins (PG).

- Both the gastric and intestinal mucosa synthesis **PGE and PGI** reduce the secretion of gastric acid and at lower concentrations may promote cytoprotection by acting on EP3 receptors.
- Analogues of **PGE1 (Misoprostol)** and of **PGE2 (Enprostil, Arbaprostil, Rioprostil),** given orally, produce similar effects.
- The protective effect lasts for hours.
- Diarrhoea
- Prevent ulceration and bleeding large doses of **Aspirin or NSAID.**

# ANTACIDS

- **Neutralize gastric acid & raise pH of gastric contents.**
- **Peptic activity** reduced if the pH rises above 4,
- **Pepsin dissociates** below pH 5
- Optimum peptic activity **pH 2 to 4.**
- **Do not decrease acid production**;
- Raises antral **pH to > 4** evoke **reflex gastrin release**
- Acid is secreted – Hyperacidity and duodenal ulcer
- “Acid rebound" occurs & gastric motility is increased.

# POTENCY

- Acid neutralizing capacity (ANC), which is defined as number of mEq
- **1 N HCl that are brought to pH 3.5 in 15 min (unit dose)**
- Rate at which it dissolves and reacts with HCl.
- Taken in empty stomach **acts for 30- 60 min** (Gastric content is passed into duodenum)
- Taken with meals **2-3 hr.**

# SYSTEMIC ANTACIDS

Sodium bicarbonate, Sodium citrate

water soluble, acts instant,

duration of action short.

neutralizer (**1 g -12 mEq HCl**), pH may rise above 7.

Demerits:

(a) Absorbed systemically: large doses **alkalosis.**

(b) Produces **CO2** in stomach

distention, discomfort, belching, Ulcer perforation.

(c) **Acid rebound** occurs

(d) **Increases Na+ load**: may worsen edema and CHF.

# NONSYSTEMIC ANTACIDS

- Insoluble and poorly absorbed
- React in stomach to form chloride salt.
- The chloride salt again reacts with the intestinal bicarbonate so that HC03 is not spared for absorption-no acid-base disturbance occurs.
- Mag. Hydroxide low concentration of OH- ions
- HCl promptly (1 g – 30 mEq HCl).
- Rebound acidity is mild and brief.
- MILK OF MAGNESIA

# Antacid combinations

(a) Fast (Mag. hydrox.) and slow (Alum. hydrox.) prompt as well as sustained effect.

(b) Mag. salts are laxative, while alum. salts are constipating: Bowel movement least affected.

(c) Gastric emptying is least affected;

(d) Dose of individual components is reduced;

ACIDIN: Mag. carbo 165 mg, dried alum. hydrox. gel 232 mg, cal. carbo 165 mg, sod. bicarb. 82 mg, with kaolin 105 mg and belladonna herb 30 pg per tab.

# ULCER PROTECTIVES- Sucralfate

- It is a basic aluminium salt of sulfated sucrose
- Sucralfate polymerizes at pH < 4 by cross linking of molecules,
- Sticky gel-like consistency.
- Adheres to ulcer base, remain there for - 6 hours.
- It precipitates surface proteins acts as a physical barrier preventing acid, pepsin and bile from coming in contact with the ulcer base.
- Has no acid neutralizing action, but delays gastric emptying
- Augmented gastric mucosal PG synthesis physical protective action

# Antimicrobials

- Effective against H. pylori are:

Amoxicillin, clarithromycin, tetracycline and metronidazole/ tinidazole.

single drug is relatively ineffective.

Resistance develops rapidly.

- A number of 2-drug and 3-drug regimens of 1 or 2 weeks duration have been tested reporting
- 60- 96% eradication rates, but the optimum regimen
- Some of the 2 week regimens are:

**Two week regimens (mg)**

1. Amoxicillin 750 + Tinidazole 500 + Omeprazole 20 all BD
2. Amoxicillin 750 + Tinidazole 500 + Lansoprazole 30 all BD
3. Clarithromycin 250 + Tinidazole 500 + Lansoprazole 30 all BD
4. Clarithromycin 500 + Amoxicillin 1000 + Lansoprazole 30 all BD
5. Clarithromycin 500 BD/Amoxicillin 750 BD + Omeprazole 20 BD
6. Amoxicillin 500 TDS/Tetracycline 500 QID + Metronidazole 400 QID/ Tinidazole 500 BD + Bismuth 120 QID
7. Amoxicillin 750 TDS + Metronidazole 500 TDS + Ranitidine 300 OD
8. Amoxicillin 750 BD + Clarithromycin 250 BD + Lansoprazole 30 BD

# LAXATIVES
# (Aperients, Purgatives, Cathartics)

- Promote evacuation of bowels.
- According to the intensity of action.

Laxative or aperients:

Milder action, elimination of soft stools.

Purgative or cathartic:

Stronger action in more fluid evacuation.

Bulk forming

Dietary fiber: Bran, Psyllium (Plantago), Ispaghula, Methylcellulose

Stool softener

Docusates (DOSS), Liquid paraffin

Stimulant purgatives

(a) Diphenylmethanes

Phenolphthalein, Bisacodyl, Sodium picosulfate

(b) Anthraquinones (Emodins)

Senna, Cascara sagrada

(c) 5-HT4 agonist

Tegaserod

(d) Fixed oil

Castor oil

## Osmotic purgatives

- Magnesium salts: sulfate, hydroxide
- Sodium salts: sulfate, phosphate
- Sod. pot. tartrate
- Lactulose

# MECHANISM OF ACTION- Purgatives Increase the water content of faeces

(a) A hydrophilic or osmotic action, retaining water and electrolytes in the intestinal lumen-increase volume of colonic content and make it easily propelled.

(b) Acting on intestinal mucosa, decrease net absorption of water and electrolyte; intestinal transit is enhanced indirectly by the fluid bulk.

(c) Increasing propulsive activity as primary action-allowing less time for absorption of salt and water as a secondary effect.

# Laxatives modify the fluid dynamics of the mucosal cell and may cause fluid accumulation in gut lumen

(a) Inhibiting Na+K+ATPase of villous cells impairing electrolyte and water absorption.

(b) Stimulating adenylyl cyclase in crypt cells increasing water and electrolyte secretion.

(c) Enhancing PG synthesis in mucosa which increases secretion.

(d) Structural injury to the absorbing intestinal mucosal cells.

# Dietary fibre:

- Bran - consists of unabsorbable cell wall
- Vegetable food- cellulose, pectins, glycoproteins and other polysaccharides.
- It absorbs water in the intestines, swells, increases water content of faeces-softens it and facilitates colonic transit.
- Osmotically active products may be formed in the colon by bacterial degradation of pectins, etc. which act to retain water.
- Dietary fibres (gums, lignins, pectins) bind bile acids and promote their excretion in faeces
- Degradation of cholesterol in liver is enhanced --- plasma LDL cholesterol is lowered.

# Psyllium (Plantago) and Ispaghula

Natural colloidal mucilage which forms a gelatinous mass by absorbing water

3-12 g of refined husk mixed with water or milk and taken daily-acts in 1-3 days.

It should not be swallowed dry

(may cause esophageal impaction).

# STOOL SOFTENER

## Docusates (Dioctyl sodium sulfosuccinate):

- It is an anionic detergent, softens the stools by net water accumulation in the lumen by an action on the intestinal mucosa.
- It emulsifies the colonic contents and increases penetration of water into faeces.
- By a detergent action, it can disrupt the mucosal barrier and enhance absorption of many nonabsorbable drugs, e.g. liquid paraffin
- Should not be combined with it.

# STIMULANT PURGATIVES

- Irritate the intestinal mucosa
- Increase motility by acting on myenteric plexuses,
- Accumulation of water and electrolytes in the lumen by altering absorptive and secretory activity of the mucosal cell.
- Inhibit Na+K+ATPase , Secretion is enhanced by activation of cAMP in crypt cells and by increased PG synthesis.

# Diphenylmethanes

- Phenolphthalein is an indicator and is in use as purgative from the beginning of the 20th century.
- It turns urine pink if alkaline.
- Bisacodyl is activated in the intestine by deacetylation.
- Action is in the colon: irritate the mucosa, produce mild inflammation and secretion.
- Bisacodyl 5-15 mg: DULCOLAX 5 mg tab; 10 mg (adult), 5 mg (child) suppository

# Anthraquinones

- Senna -leaves and pod- Cascara sagrada is the powdered bark of the buck-thorn tree
- Anthraquinone glycosides, also called emodins.
- Unabsorbed in the small intestine,
- They are passed to the colon where bacteria liberate the active anthrol form,
- which either acts locally or is absorbed into circulation-excreted in bile to act on small intestine.
- Thus, they take 6-8 hours to produce action.

# Castor oil

- It is one of the oldest purgatives.
- Castor oil - bland vegetable oil obtained from the seeds of Ricinus communis;
- Triglyceride of ricinoleic acid which is a polar long chain fatty acid.
- Castor oil is hydrolysed in the ileum by lipase to ricinoleic acid and glycerol.
- Irritate the mucosa and stimulate intestinal contractions

# OSMOTIC PURGATIVES

- Solutes that are not absorbed in the intestine

  retain water osmotically

  Distend the bowel-increasing peristalsis indirectly.
- Magnesium ions release cholecystokinin which may aid purgative action of Mag. salts

- Mag. sulfate (Epsom salt): 5-15 g; bitter in taste.
- Mag. hydroxide (as 8% W /W suspensionmilk of magnesia) 30 ml; bland in taste, also used as antacid.
- Sod. sulfate (Glauber's salt): 10-I5g; bad in taste.
- Sod. phosphate: 6-12 g, taste not unpleasant.
- Sod. pot. tartrate (Rochelle salt): 8-15 g, relatively pleasant tasting.
- The salts in above mentioned doses, dissolved in 150-200 ml of water, produce 1-2 fluid evacuations within 1-3 hours with mild cramping; cause nearly complete emptying of bowels.
- Mag. salts are contraindicated in renal insufficiency, while Sod. salts should not be CHF
- They may be preferred for preparation of bowel before surgery and colonoscopy; in food/drug poisoning and as after-purge in treatment of tapeworm infestation.

**Table 48.1:** Type of stools and latency of action of purgatives employed in usually recommended doses

| *Soft, formed faeces (take 1–3 days)* | *Semifluid stools (take 6–8 hrs)* | *Watery evacuation (within 1–3 hrs)* |
|---|---|---|
| Bulk forming | Phenolphthalein | Saline purgatives |
| Docusates | Bisacodyl | Castor oil |
| Liquid paraffin | Sod. picosulfate | |
| Lactulose | Senna | |

# Lactulose

- Semisynthetic disaccharide of fructose and lactose
- It is neither digested nor absorbed in the SI –retains water.
- Broken down in the colon by bacteria to osmotically more active products.
- The breakdown products of lactulose are acidic-reduce the pH of stools
- In a dose of 10 g BO taken with plenty of water, it produces soft formed stools in 1-3 days.
- Flatulence and flatus is common, cramps.
- Lactulose causes reduction of blood NH3 concentration by 25-50% in patients with hepatic encephalopathy.

# Functional constipation

- Hard stools requiring straining to pass, or a sense of incomplete evacuation.
- Inadequate fibre in diet, less fluid intake.
- Lack of exercise, sedentary nature of work.
- Irregular bowel habits, rushing out for job.

# Bedridden patients

(myocardial infarction, stroke, fractures, postoperative)

- Bowel movement may be sluggish and constipation
- To prevent constipation: Give bulk forming agents on a regular schedule; docusates, lactulose and liquid paraffin are alternatives.
- To treat constipation: Enema (soap-water / glycerine) is preferred; bisacodyl or senna may be used.
- To avoid straining at stools (hernia, cardiovascular disease, eye surgery) and in perianal afflictions (piles, fissure, anal surgery)

# Preparation of bowel for surgery, colonoscopy, abdominal X-ray

- Bowel needs to be emptied of the contents including gas.
- Saline purgative, bisacodyl or senna may be used;
- castor oil only in exceptional circumstances.

- After certain anthelmintics (especially for tapeworm) Saline.
- purgative or senna may be used to flush out the worm and the anthelmintic drug.

# Food/drug poisoning

- Drive out the unabsorbed irritant/poisonous material from the intestines.
- Only saline purgatives are satisfactory.
- The choice of a purgative depends on the
- latency of action and type of stools desired.

# Purgative abuse

- Obsessed with using purgatives regularly.
- Reflection of a psychological problem.
- Habit forms, it is difficult to break.
- Dangers of purgative abuse are:

  1. Flairing of intestinal pathology, rupture of inflamed appendix.

  2. Fluid and electrolyte imbalance, especially hypokalaemia.

  3. Steatorrhoea, malabsorption syndrome.

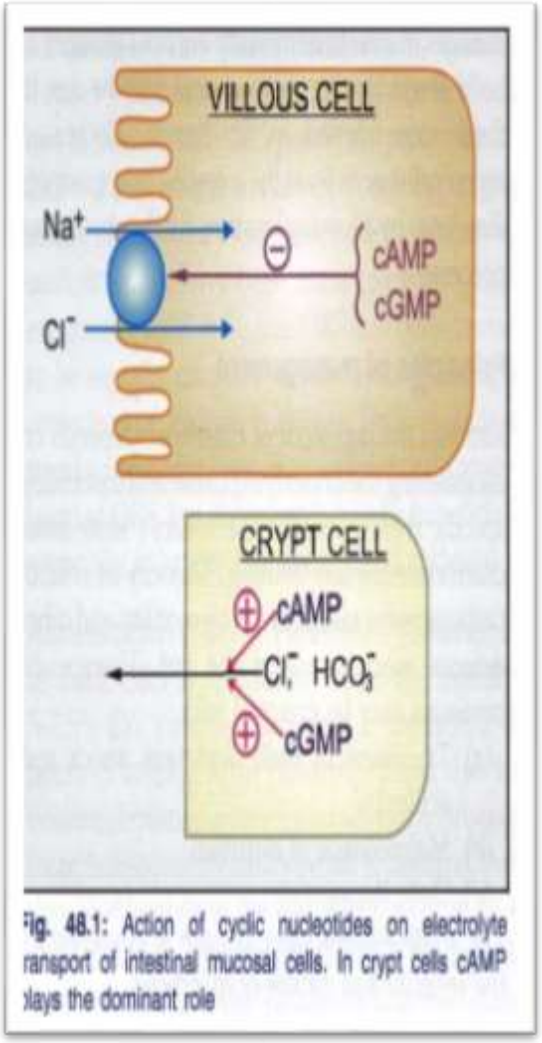
  4. Protein losing enteropathy.

  5. Spastic colitis.

- Diarrhoea is too frequent, often too precipitate passage of poorly formed stools. In pathological terms, it occurs due to passage of excess water in faeces.
- More than 5 million children under the age of 5 years die every year due to diarrhoea.
- A nationwide study has estimated that diarrhoea kills> 1 million children in lndia annually

- Water and electrolytes are absorbed as well as secreted in the intestine.
- In the ileum and colon active Na+K+ATPase mediated salt absorption occurs, primarily in the mature cells lining the villous tips, water follows isoosmotically.
- Inhibition of Na+K+ATPase and structural damage to mucosal cell (by Rota virus) causes diarrhoea by reducing absorption.

- Intracellular cyclic nucleotides are important regulators of absorptive and secretory processes.
- Stimuli enhancing cAMP or cGMP cause net loss of salt and water, both by inhibiting NaCl absorption in villous cells and by promoting anion secretion (Na+ accompanies) in the crypt cells which are primarily secretory.




ig. 48.1: Action of cyclic nucleotides on electrolyte ransport of intestinal mucosal cells. In crypt cells cAMP lays the dominant role

- Many bacterial toxins, e.g. cholera toxin, exotoxin elaborated by Enterotoxigenic E. coli (ETEC), Staph. aureus, Salmonella, etc. activate adenylyl cyclase which enhances secretion that reaches its peak after 3-4 hours
- Concurrent inhibition of absorption adds to the rate of salt and water loss.

- Diarrhoea associated with carcinoid (secreting 5-HT) and medullary carcinoma of thyroid (secreting calcitonin) is mediated by cAMP. Excess of bile acids also cause diarrhoea by activating adenylyl cyclase.

# Principles of management

- Treatment of fluid depletion, shock and acidosis.
- Maintenance of nutrition.
- Drug therapy.

# REHYDRATION

- Intravenous rehydration
- It is needed only when fluid loss is severe
- i.e., > 10 ml/kg/hr, or is unable to take enough oral fluids due to weakness, stupor or vomiting.
- i.v. fluid (Dhaka fluid) is: NaCl 85 mM = 5 g

  KCl 13 mM = 1 g NaHC03 48 mM = 4 g.
- In 1 L of water or 5% glucose solution

## New formula WHO-ORS

| *Content* | | *Concentrations* | |
|---|---|---|---|
| NaCl | : 2.6 g | $Na^+$ | — 75 mM |
| KCl | : 1.5 g | $K^+$ | — 20 mM |
| Trisod. citrate | : 2.9 g | $Cl^-$ | — 65 mM |
| Glucose | : 13.5 g | Citrate | — 10 mM |
| Water | : 1 L | Glucose | — 75 mM |

Total osmolarity 245 mOsm/L

(available as ORETRAL-A, ELECTROBION, ELECTRAL

| | Organism | Blood | Polymorphs in stool | Vomiting in stool | Drugs recommended |
|---|---|---|---|---|---|
| **I** | **Bacterial:** | | | | |
| | *Shigella* | + | +++ | +++ | Ciprofloxacin; Norfloxacin; Cotrimoxazole; Nitazoxanide |
| | *Salmonella* (non-typhi species) | + | +++ | + | Cotrimoxazole; Fluoroquinolone or Ceftriaxone in severe cases |
| | *E. coli* | ++ | ++ | + | Fluoroquinolone; Cotrimoxazole |
| | *E. coli (Shiga toxin producing)* | +++ | ± | + | Avoid antimotility drugs |
| | *Vibrio* | ± | ± | ± | Doxycycline; Fluoroquinolone |
| | *Campylobacter* | + | ++ | + | Azithromycin |
| | *Cl. difficile* | + | +++ | - | Metronidazole |
| **II** | **Protozoal:** | | | | |
| | *E.histolytica* | ± | ± | ± | Metronidazole |
| | *Giardia* | - | - | ± | Metronidazole |
| | *Cryptosporidium* | - | - | - | Azithromycin; Nitazoxanide |
| | *Cyclospora* | - | - | + | Cotrimoxazole |
| **III** | **Viral:** | - | - | ++ | No antimicrobial |

**Table 48.2:** Nonspecific antidiarrhoeal agents and their indications

| *Class* | *Drug* | *Use* |
|---|---|---|
| ABSORBANTS | Ispaghula, Psyllium, Methyl cellulose | Irritable bowel syndrome (IBS), Ileostomy/colostomy diarrhoea |
| ANTISECRETORY | Sulfasalazine, Mesalazine | Ulcerative colitis, Other inflammatory bowel diseases (IBD) |
| | Bismuth subsalicylate | Travellers' diarrhoea |
| | Atropine | Nervous, drug induced diarrhoea |
| | Octreotide | Carcinoid, VIP secreting tumour, diarrhoea in AIDS |
| | Racecadotril | Acute secretory diarrhoeas |
| ANTIMOTILITY (Opioids) (also antisecretory) | Codeine, Diphenoxylate-atropine, Loperamide | Noninfective or mild travellers' diarrhoea; Idiopathic diarrhoea in AIDS, After anal surgery, colostomy. |

# EMESIS

- Vomiting occurs due to stimulation of the emetic centre situated in the medulla oblongata.
- Multiple pathways can elicit vomiting
- The chemoreceptor trigger zone (CTZ) located in the area postrema and the nucleus tractus solitarius (NTS) are the most important relay areas for afferent impulses arising in the g.i.t, throat and other viscera.

Cytotoxic drugs, radiation and other g.i. irritants
release 5-HT from enterochromaffin cells

acts on 5-$HT_3$ receptors present on extrinsic primary afferent neurones (PAN) of the enteric nervous system (ENS),

send impulses to NTS and CTZ.

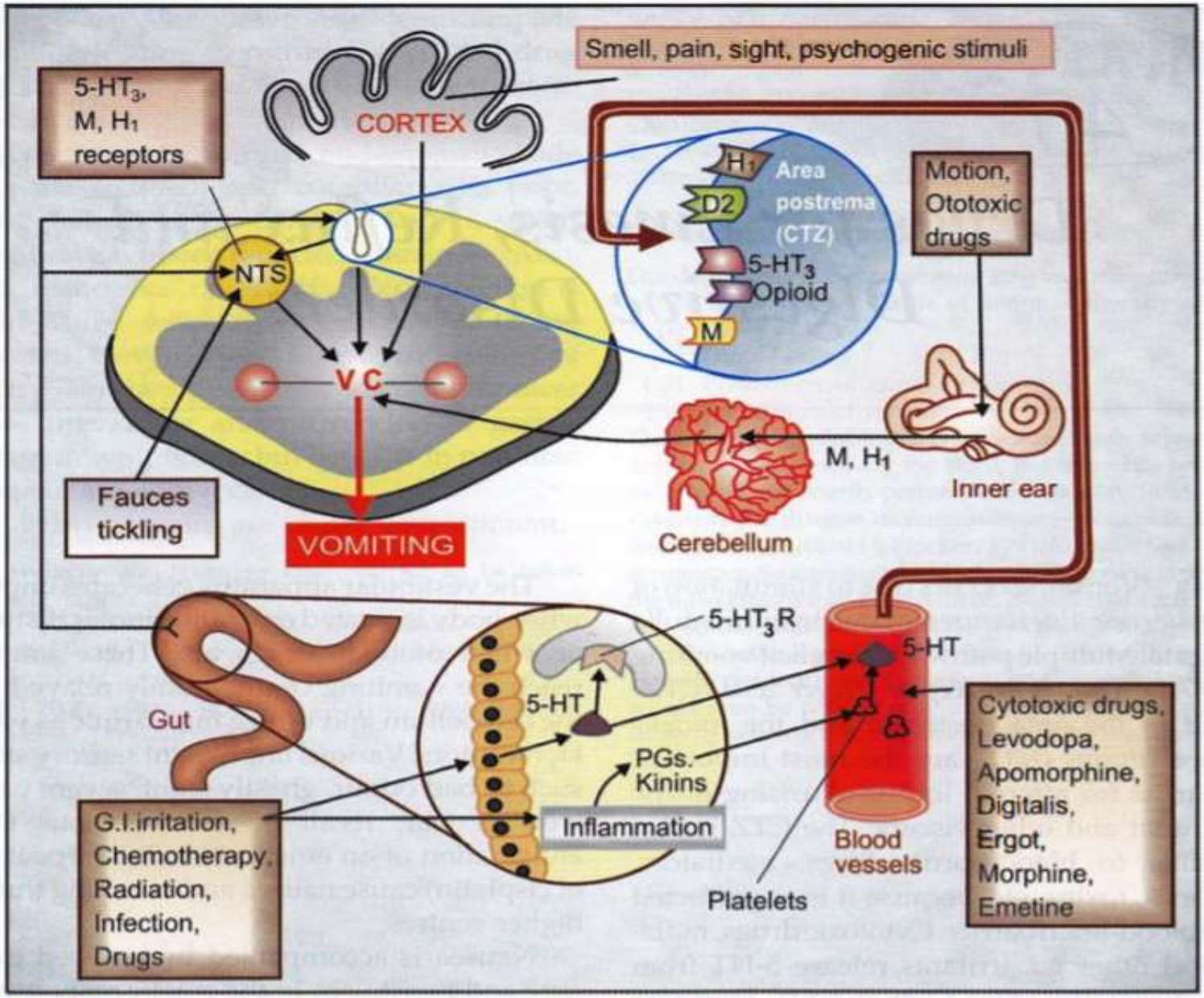



**Fig. 47.1:** Major central and visceral structures involved in emesis and the neurohumoral receptors mediating the emetic response. NTS: Nucleus tractus solitarius; VC: Vomiting centre; CTZ---Chemoreceptor trigger zone; 5-$HT_3$R: 5-$HT_3$ receptor

- Vomiting needs to be induced only when an undesirable substance (poison) has been ingested.
- Powdered mustard suspension or strong salts solution may be used in emergency.
- They act reflexly by irritating the stomach.

# Ipecacuanha

- The dried root of *Cephaelis ipecacuanha* contains emetine and is used as syrup ipecac (15-30 ml in adults, 10-15 ml in children, 5 ml in infants) for inducing vomiting.
- It should be available in every household for emergency use.

# Apomorphine

- It is a semisynthetic derivative of morphine; acts as a dopaminergic agonist on the CTZ. Injected i.m./s.c. in a dose of 6 mg, it promptly (within 5 min) induces vomiting.

# All emetics are contraindicated

Corrosive (acid, alkali) poisoning: injury to esophageal mucosa.

CNS stimulant drug poisoning: convulsions

Kerosene poisoning: chemical pneumonia

Unconscious patient: may aspirate the vomitus, because laryngeal reflex is likely to be impaired.

Morphine or phenothiazine poisoning

# ANTIEMETICS

These are drugs used to prevent or suppress vomiting.

## CLASSIFICATION

| | | |
|---|---|---|
| 1. | *Anticholinergics* | Hyoscine, Dicyclomine |
| 2. | *$H_1$ antihistaminics* | Promethazine, Diphenhydramine, Dimenhydrinate, Doxylamine, Cyclizine, Meclozine, Cinnarizine. |
| 3. | *Neuroleptics ($D_2$ blockers)* | Chlorpromazine, Prochlorperazine, Haloperidol, etc. |
| 4. | *Prokinetic drugs* | Metoclopramide, Domperidone, Cisapride, Mosapride Tegaserod |
| 5. | *5-$HT_3$ antagonists* | Ondansetron, Granisetron |
| 6. | *Adjuvant antiemetics* | Dexamethasone, Benzodiazepines, Cannabinoids. |

# ANTICHOLINERGICS

- Hyoscine (0.2-0.4 mg oral, i.m.)
- Motion sickness.
- Produces sedation and other anticholinergic side effects
- Blocking conduction of nerve impulses across a cholinergic link in the pathway leading from the vestibular apparatus to the vomiting centre
- A transdermal patch 1.5 mg of hyoscine, 3 days Applied behind the pinna

# H1 ANTIHISTAMINICS

- Promethazine
- 4-6 hours, sedation and dryness of mouth.
- By their central anticholinergic action they block the extrapyramidal side effects of metoclopramide while supplementing its antiemetic action.
- Chemotherapy induced vomiting.

# Doxylamine

- H1 antihistaminic with prominent anticholinergic activity.
- Marketed in combination with pyridoxine, it is specifically promoted in India for 'morning sickness' (vomiting of early pregnancy)
- Foetal malformation

# NEUROLEPTICS

- These are potent antiemetics
- Act by blocking D2 receptors in the CTZ
- Antagonize apomorphine induced vomiting and have additional antimuscarinic as well as $H_1$ antihistaminic property

- Drug induced and postanaesthetic nausea and vomiting
- Disease induced vomiting: gastroenteritis, uraemia, liver disease, migraine, etc.
- Malignancy associated and cancer chemotherapy induced vomiting.
- Radiation sickness vomiting
- Morning sickness: should not be used except in hyperemesis gravidarum.

# PROKINETIC DRUGS

- These are drugs which promote gastrointestinal transit and speed gastric emptying by enhancing coordinated propulsive motility.

# GIT

- It has more prominent effect on upper g.i.t.;
- Increases gastric peristalsis
- relaxing the pylorus and the first part of duodenum
- speeds gastric emptying,
- This action is independent of vagal innervation,
- Lower esophageal sphincter (LES) tone is increased and gastroesophageal reflux is opposed
- Increases intestinal peristalsis to some extent, but has no significant action on colonic motility and gastric secretion.

- Metoclopramide acts through both dopaminergic and serotonergic receptors
- D2 antagonism
- 5-HT4 agonism
- 5-HT3 antagonism

# 5-HT3 ANTAGONISTS

- Ondansetron
- Cancer chemotherapy/radiotherapy induced vomiting, and postoperative nausea and vomiting as well.
- It blocks the depolarizing action of 5-HT through 5-HT3 receptors on vagal afferents in the g.i.t. as well as in NTS and CTZ.

# Acknowledgement


- The Presentation is being used for educational and non commercial Purposes
- Thanks are due to all the original contributors and entities whose pictures were used in the creation of this presentation.