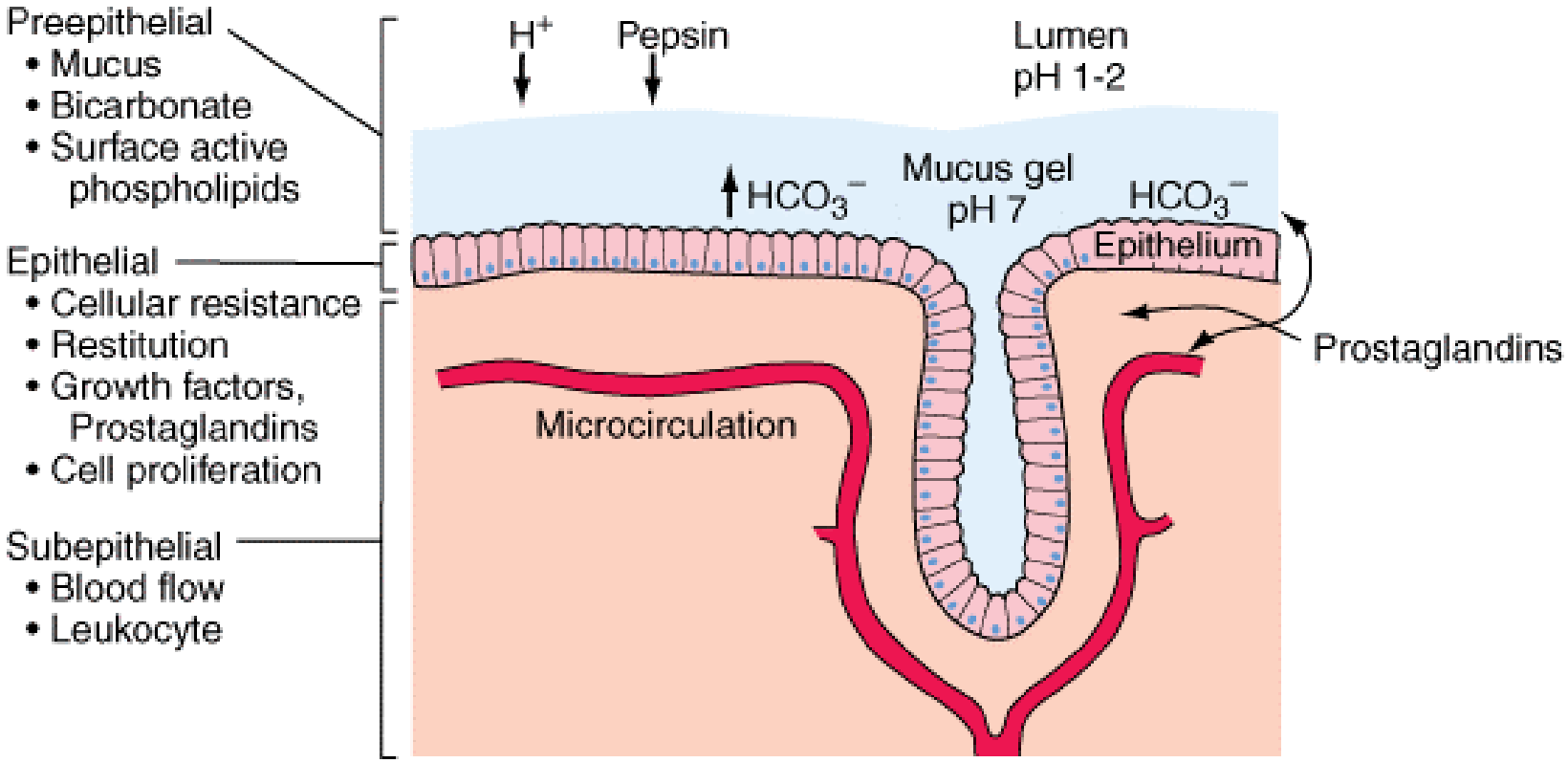
Mucosal Protective Agents



1-Both mucus and epithelial cell-cell tight junctions restrict back diffusion of acid and pepsin.

2-Epithelial bicarbonate secretion

3-Blood flow carries bicarbonate

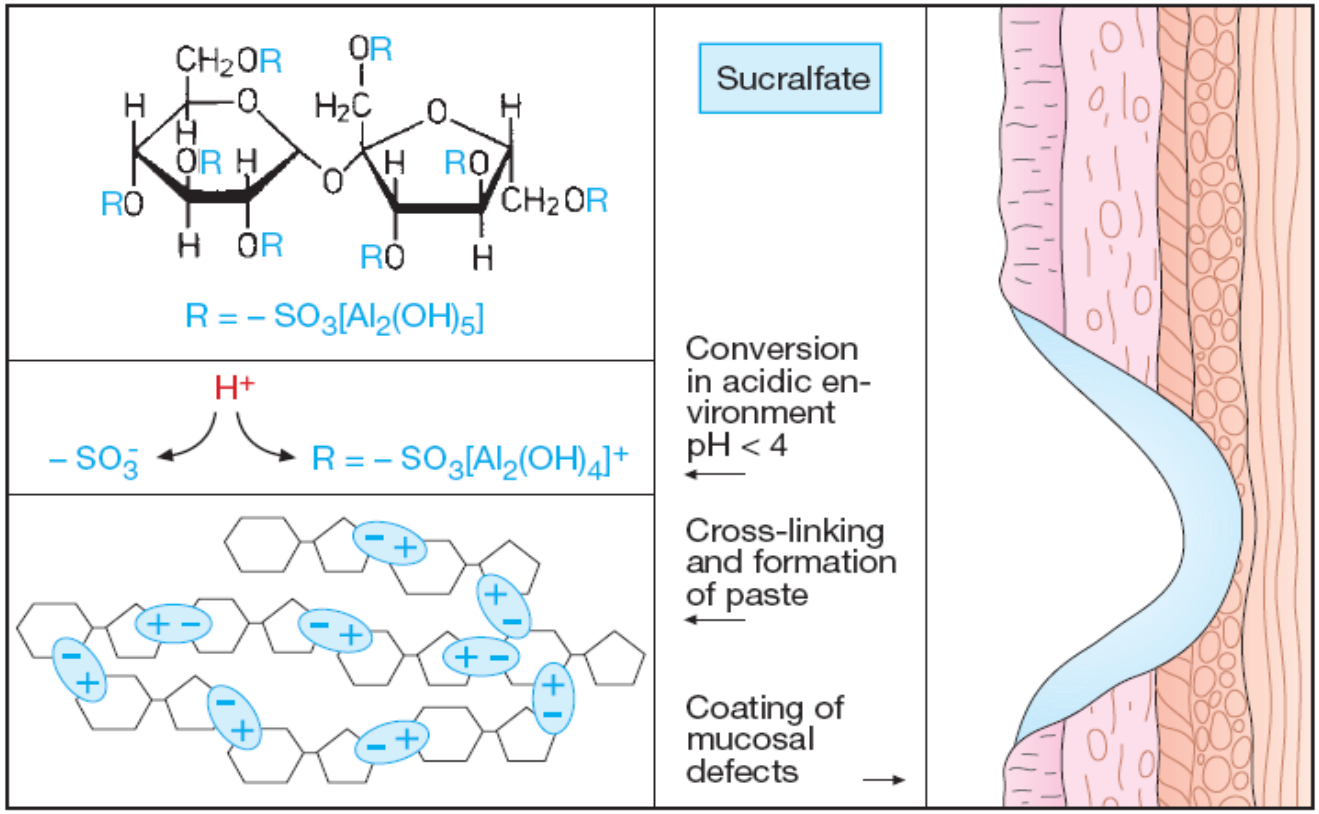
4- injured epithelium are repaired by **restitution**

5- Mucosal prostaglandins stimulates mucus and bicarbonate secretion and mucosal blood flow.

Sucralfate

A salt of sucrose complexed to sulfated aluminum hydroxide.

In the stomach, It breaks down into sucrose sulfate (strongly negatively charged) and an aluminum salt.



A. Chemical structure and protective effect of sucralfate

The **negatively** charged sucrose sulfate binds to **positively** charged proteins in the base of ulcers or erosion, forming a **physical barrier** that restricts further caustic damage and **stimulates mucosal prostaglandin and bicarbonate secretion**.

- Acts for 6 hours.
- Less than 3% of intact drug and aluminum is absorbed.

Clinical Uses

1 g four times daily on an empty stomach (through a nasogastric tube) reduces the incidence of upper GI bleeding in critically ill patients hospitalized in the intensive care unit.

Prevention of **stress-related bleeding** because acid inhibitory therapies may increase the risk of nosocomial pneumonia (an infection of the lungs that occurs during a **hospital** stay). *IV H2 blockers and PPI prevent bleeding but these two agents decrease the acidity of the stomach which is considered the first line of defense.There for it's better to use Sucralfate since it won't affect the acidity.*

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Adverse Effects

Not absorbed, so no systemic adverse effects.

Constipation (2%) due to the aluminum salt.

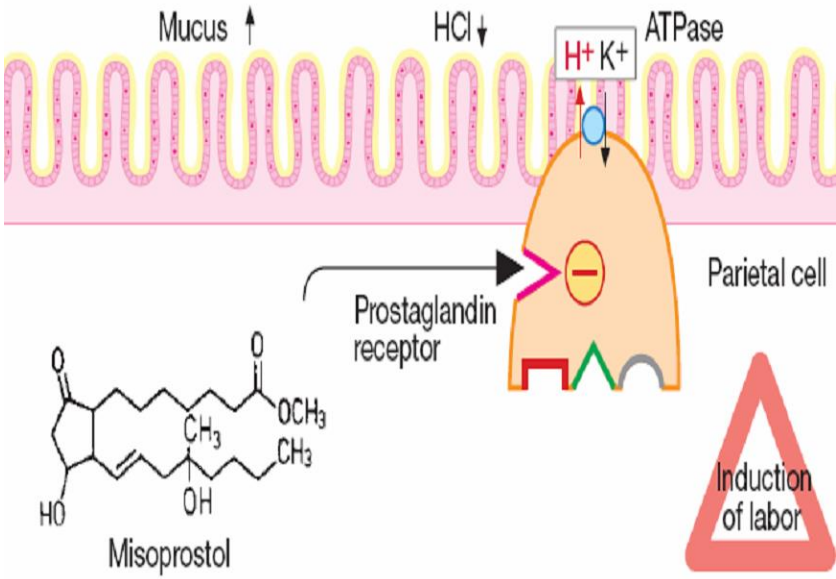
Caution in renal insufficiency.

Drug Interactions

٢٠ Sucralfate may bind to other medications, impairing their absorption.

Prostaglandin Analogs

Misoprostol



A methyl analog of **PGE1.**

Half-life is less than 30 min

Administered 3-4 times daily.

1-Stimulates mucus & bicarbonate *Secretion. Recommended for Patients who are forced to take NSAID which cause damage to The mucosa*

2- Enhances mucosal blood flow.

3- Acts on parietal cells, reducing histamine-stimulated cAMP production and causing **modest acid inhibition**.

4- Stimulates **intestinal** electrolyte & fluid secretion,

5- Increase intestinal motility >*causes diarrhea*

6- **Uterine contractions**.>*not given in case of pregnancy*

Clinical Uses of Prostaglandin Analogs:

Prevention of NSAID-induced ulcers in high-risk patients.

Not widely used for this purpose because of:

a- side effects.

b. need for multiple daily dosing.

c. **PPI** may be as effective and better tolerated.

d. Cyclooxygenase2-selective NSAIDs
an option for such patients**.** are

Adverse Effects & Drug Interactions

Diarrhea and cramping abdominal pain (10–20%).

it should not be used during pregnancy

No significant drug interactions.

Colloidal Bismuth Compounds:

Bismuth subsalicylate.

Bismuth subcitrate.

All heavy metals have antibacterial effect

Bismuth is minimally absorbed from GIT (< 1%).

A mucosal protective agent, provides coat on the ulcer.

Reduce the gastric HCL secretion.
Help in eradication of H. pylori.
Stimulates the PGE secretion.
Reduce pepsin secretion.
Decrease H+ ion back diffusion.

Bismuth subsalicylate reduces stool frequency and liquidity in acute infectious diarrhea, due to salicylate inhibition of intestinal prostaglandin and chloride secretion.

Has direct antimicrobial effects & binds enterotoxins, so useful in preventing & treating **traveler's diarrhea**.

Widely used for the nonspecific treatment of dyspepsia and acute diarrhea.

Has direct antimicrobial activity against *H pylori and* used as second-line therapy for the eradication of *H pylori* infection

PPI with bismuth subsalicylate , tetracycline and metronidazole for 10–14 days).

Adverse Effects

Blackening of the stool and the tongue.

Prolonged usage may rarely lead to bismuth toxicity, resulting in **encephalopathy**.

Drugs Stimulating GI Motility

(**Prokinetic agents**)

Potential uses:

Increasing lower esophageal sphincter pressures, useful for GERD.

improving gastric emptying, helpful for gastroparesis (*Is when the stomach stops emptying its content and fluid is trapped inside)* and postsurgical gastric emptying delay. (*because of the effect of morphine*)

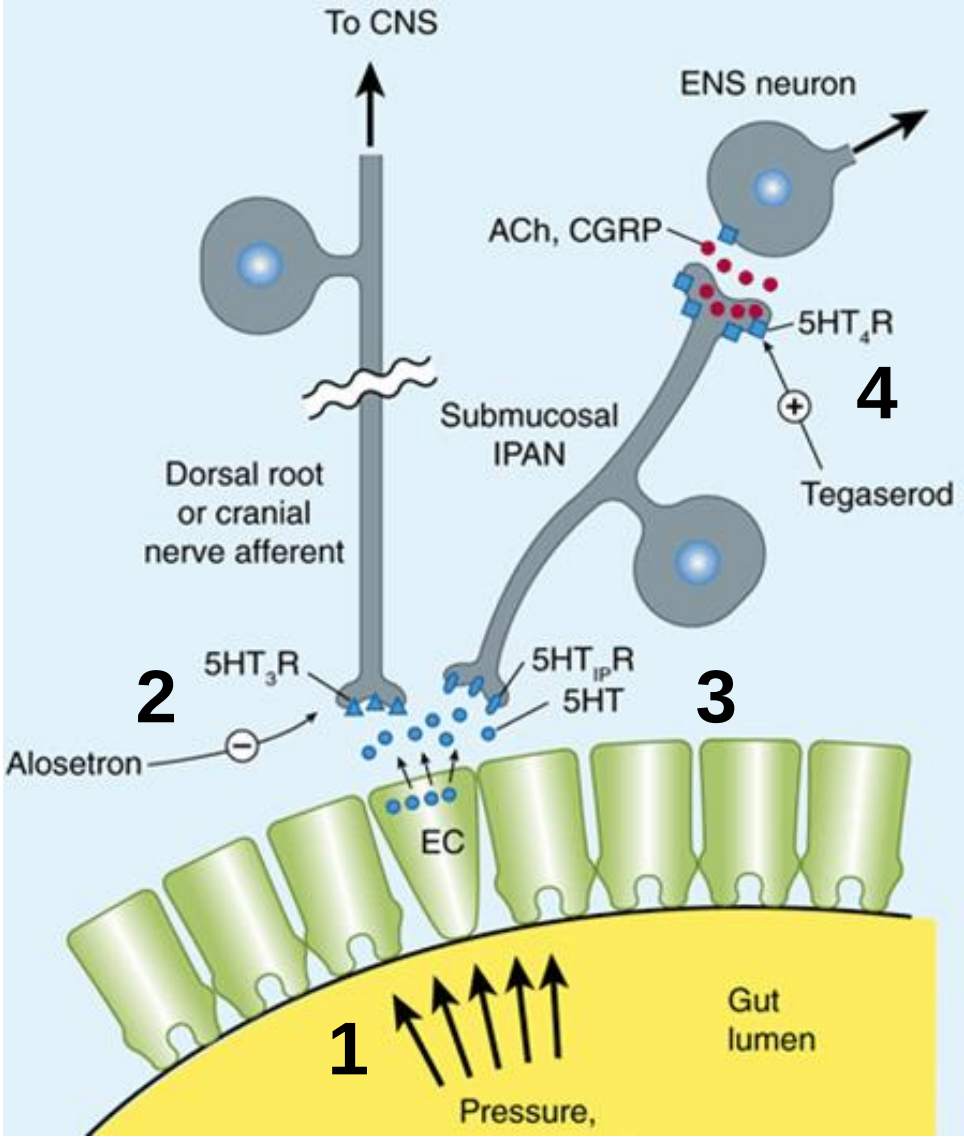
Stimulation of the small intestine useful for postoperative ileus.

enhancing colonic transit, useful in the treatment of constipation.

1-Gut distention stimulates 5-HT release from EC cells.

2-Stimulation of **5-HT3** receptors on the extrinsic afferent nerves, stimulate **nausea, vomiting**, or **abdominal pain**.

3- 5-HT also stimulates **5-HT1P** receptors of the intrinsic primary afferent nerves (IPANs) which activate the enteric neurons responsible for **peristaltic and secretory reflex activity.**



4- Stimulation of 5-HT4 receptors (5-HT4R) on presynaptic terminals of IPANs enhances release of **ACh** & calcitonin gene related peptide (**CGRP**), promoting reflex activity.

The enteric nervous system can independently regulate GI motility and secretion.

The myenteric interneurons control:

peristaltic reflex, promoting release of excitatory mediators proximally and inhibitory mediators distally.

Motilin stimulate excitatory neurons or muscle cells directly. *Can increase movement of the intestine that's why it is called motilin for motion*

Erythromycin acts as motilin agonist, sometimes used to stimulate gastrointestinal motility. Administration of a low dose of erythromycin will induce peristalsis.

Dopamine acts as an inhibitory neurotransmitter in the GIT, decreasing the intensity of esophageal and gastric contractions.

Cholinomimetic Agents

Bethanechol

Stimulates muscarinic **M3** receptors on muscle cells and at myenteric plexus synapses .

Was used for the treatment of GERD and gastroparesis.

Neostigmine

AchE inhibitor enhances gastric, small intestine, and colonic emptying.

IV neostigmine used for the treatment of acute large bowel distention (**acute colonic pseudo-obstruction**).

Administration of 2 mg results in prompt colonic evacuation of flatus (*gases*) and feces.

Cholinergic effects include excessive salivation, nausea, vomiting, diarrhea, and bradycardia. These *are used but we have better drugs with lesser side effects*.

Dopamine D2-receptor antagonists.

Metoclopramide & Domperidone

D2 Antagonists.

Dopamine acts as an inhibitory neurotransmitter in the GIT, decreasing the intensity of esophageal & gastric contractions. *So if you block dopamine receptors you will have increased motility*.

Metoclopramide & Domperidone block D2 receptors causing:

-increase esophageal peristaltic amplitude.

-increase lower esophageal sphincter pressure.*good for patients with reflux disease*.

-enhance gastric emptying.

-have no effect on small intestine or colonic motility.

Also block dopamine **D2** receptors in the **chemoreceptor trigger zone of the medulla (area postrema),** resulting in potent **anti nausea and antiemetic actions.**

Clinical Uses

Gastroesophageal Reflux Disease

Not effective with **erosive esophagitis**. *Because erosion needs strong inhibition of acid so better use PPI*.

Not superior to antisecretory agents.

Because antisecretory agents can take care of any ulcer or erosion.However in case of refractory heartburn which is not responding to antisecretory agents alone, they may combine both(D2 blocker).

Used mainly in combination with antisecretory agents in patients with **refractory heartburn**.

Impaired Gastric Emptying (Gastroparesis)

widely used in post surgical and diabetic gastroparesis

Nonulcer Dyspepsia *because they can empty the stomach quickly.*

Prevention of Vomiting

Postpartum Lactation Stimulation.

Domperidone is used to promote postpartum lactation. *Used to stimulate the release of prolactin which is inhibited by dopamine.*

Adverse Effects:

Metclopromide crosses BBB so can cause: Restlessness, drowsiness, insomnia, anxiety, agitation, extrapyramidal symptoms (dystonia *(repetitive movements of lips or hands..)*, akathisia *(inability to remain seated)* , parkinsonian features) and tardive dyskinesia.

Domperidone does not cross the BBB, so

does not cause CNS effects

Both drugs can elevate serum prolactin levels causing galactorrhea, gynecomastia, impotence and menstrual disorders.

Laxatives

Intermittent constipation is best prevented with

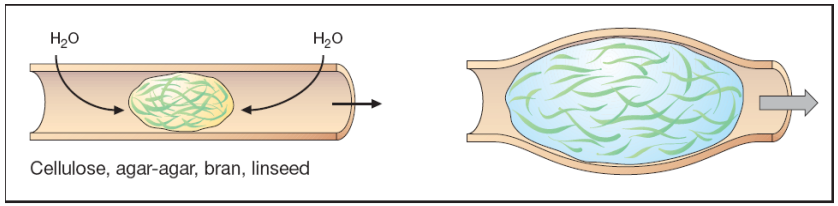
a high-fiber diet.

adequate fluid intake.

responding to nature's call.

regular exercise.

Bulk-Forming Laxatives



B. Bulk laxatives

When the absorb water they become bulky and stretch the wall. Stretching of the colon can promote evacuation.

Indigestible, hydrophilic colloids that absorb water, forming a bulky, emollient gel that distends the colon and promotes peristalsis. Effective within 1-3 days.

Include natural plant products (**psyllium, methylcellulose, bran**) and synthetic fibers **(polycarbophil).**

Bacterial digestion of plant fibers within the colon may lead to increased **bloating and flatus**.

Stool Surfactant Agents (Softeners)

Docusate

Detergents or surfactants that act as stool-wetting and stool-softening agents, allowing the mixing of water, lipids, and fecal matter.

Alters intestinal permeability and increases net water and electrolyte secretions in the intestine.

Orally: Softening of feces within **1-3 days**

Rectally: effective within **5 to 20 minutes.**

Used in symptomatic treatment of constipation & in painful anorectal conditions such as hemorrhoids and anal fissures.

Glycerin suppository.

works by irritating the lining of the intestine and increasing the amount of fluid, making it easier for stools to pass. *They absorb water from the rectum which causes irritations and this promotes defecation and makes the stool soft*

Lubricant/Emollient

Site of Action: **Colon.**

Onset of Action: 6 - 8 hours.

Causing lubrication of the stool & make it slippery, so that it slides through the intestine more easily.

It is not absorbed and increase the bulk of the intestinal contents as it reduces the water absorption

Liquid paraffin *is colorless, oily and tasteless.*

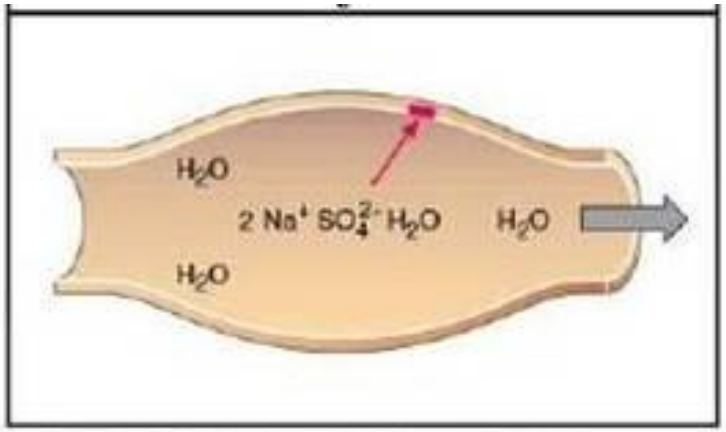
Used to prevent and treat fecal impaction.

Aspiration can result in a severe lipid pneumonitis

Long-term use can impair absorption of fat-soluble vitamins.

Not pleasant to take also it can slip out of anal sphincter and causes embarrassment. Not recommended for regular use.

Osmotic Laxatives



C. Osmotically active laxatives

Soluble but nonabsorbable compounds that result in increased stool liquidity due to an increase in fecal fluid.

Nonabsorbable Sugars or Salts

Magnesium hydroxide (milk of magnesia)

Not used for prolonged periods in renal insufficiency due to the risk of hypermagnesemia *(which has bad effects on the heart and increase BP)*.

Large doses of **magnesium citrate** & **sodium phosphate** cause Purgation: rapid bowel evacuation within1-3 h. This might cause volume depletion.

Lactulose

Disaccharide, not absorbed causing retention of water through osmosis leading to softer, easier to pass stool.

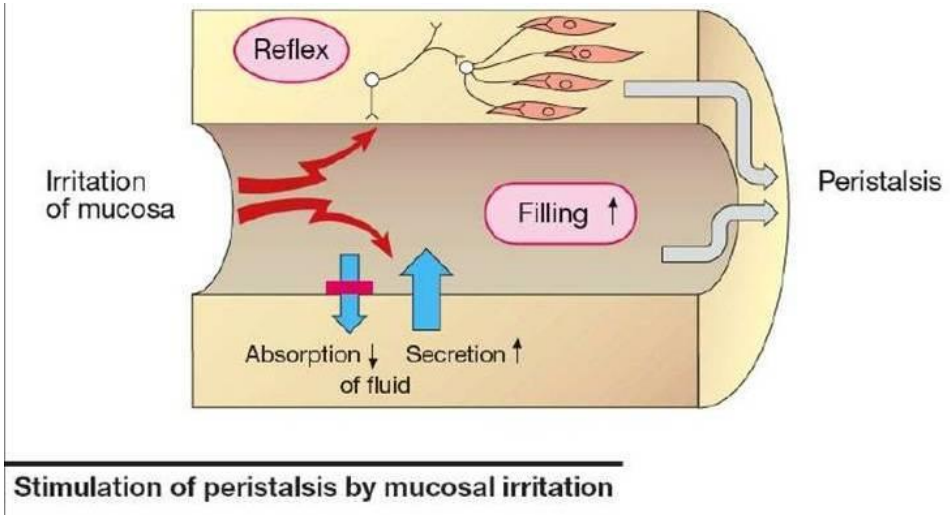
in the **colon**, it is **fermented** by the gut flora producing osmotic metabolites causing severe flatus and cramps.

Drug of choice in hepatic encephalopathy to trap NH3. *In case of liver failure, the liver no longer is able to trap NH3. Lactic acid reacts with ammonia to produce ammonium compounds which are not absorbed and so the level of ammonia in the blood is decreased.*

Lactulose is converted into lactic acid, which decreases the luminal pH. So, NH3 is trapped and prevented from absorption.

Stimulant Laxatives

Direct stimulation of the enteric nervous system and colonic electrolyte and fluid secretion.



Stimulation of peristalsis by mucosal irritation

Anthraquinone Derivatives:

Aloe, senna, and **cascara**

Occur naturally in plants.

Poorly absorbed & after hydrolysis in the colon, produce a bowel movement in 6–12 h when given orally and within 2 h when given rectally.

Chronic use leads to a brown pigmentation of the colon known As "**melanosis coli**."

Bisacodyl

Tablet and suppository for treatment of acute and chronic constipation

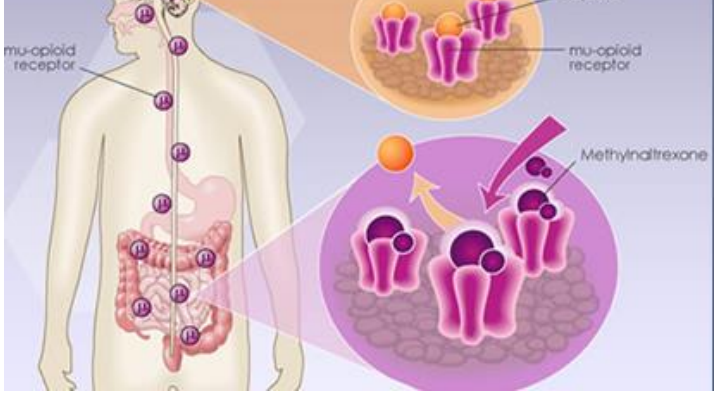
induces bowel movement within 6–10 h orally and 30–60 minutes rectally.

Safe for acute and long-term use

Phenolphthalein

Removed from the market owing to concerns about possible cardiac toxicity*. However, it has the advantage of being tasteless.*

Opioid Receptor Antagonists



Do not cross the BBB.

Block peripheral (**μ**) mu – opioid receptors without central analgesic effects.

Mu receptors are both found centrally and peripherally. So although the drug doesn't cross the BBB it does act on the brain through the peripheral mu receptor.

Methylnaltrexone

Used for opioid - induced constipation in patients with advanced illness not responding to other agents *because they patients usually take morphine which causes constipation*. S.C. injection every 2 days.

Alvimopan

Short-term use for postoperative ileus in hospitalized patients.

Given orally within 5 hours before surgery and twice daily after surgery until bowel function has recovered, but for no more than 7 days, because of possible cardiovascular toxicity.