
بسم الله الرحمن الرحيم

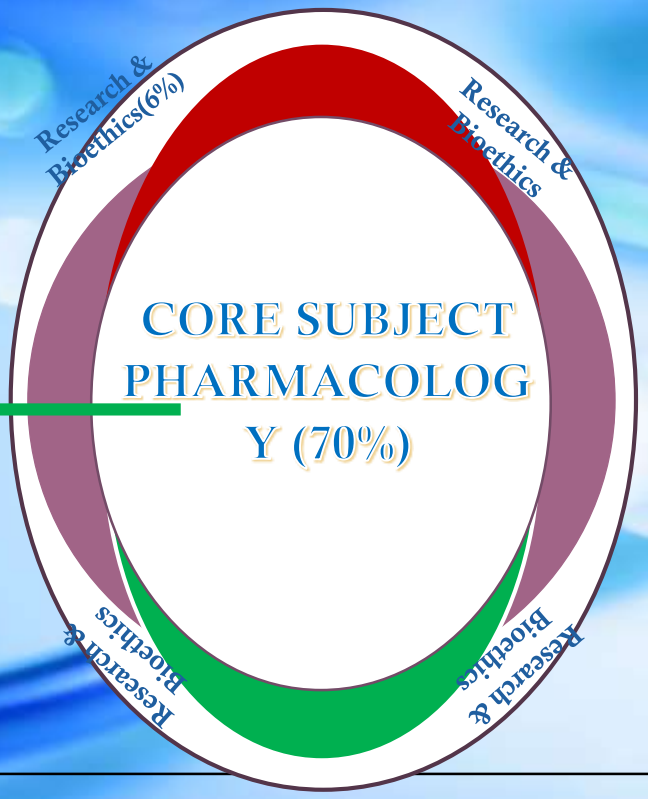
MOTTO AND VISION

- To impart evidence based research oriented medical education
- To provide best possible patient care
- To inculcate the values of mutual respect and ethical practice of medicine

PROFESSOR UMAR'S CLINICALLY ORIENTED INTEGRATION MODEL FOR BASIC SCIENCES INTERACTIVE LECTURES

VERTICAL INTEGRATION
Clinical Subjects (18%)

SPIRAL INTEGRATION ANATOMY / PHYSIOLOGY (6%)



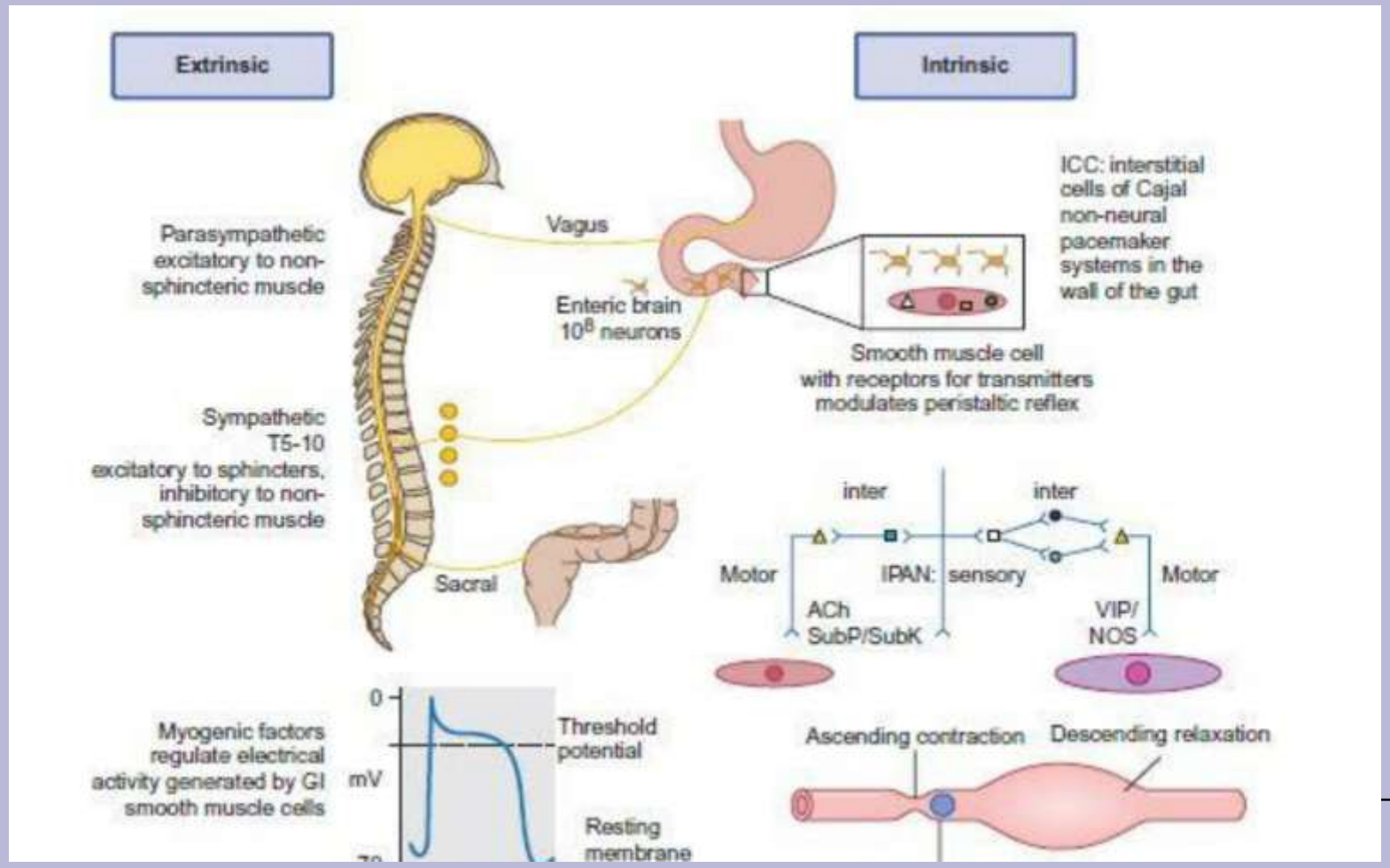
3rd Year Pharmacology LGIS(17 slides)	
Core Subject – 19slides (70%)	
Spiral Integration (anatomy/physiology)– (1 slide) (4%)	
Vertical integration (Clinical Subjects)	• (Medicine) – 3 slides (10%)
Research & Bioethics 1 slide(6%)	

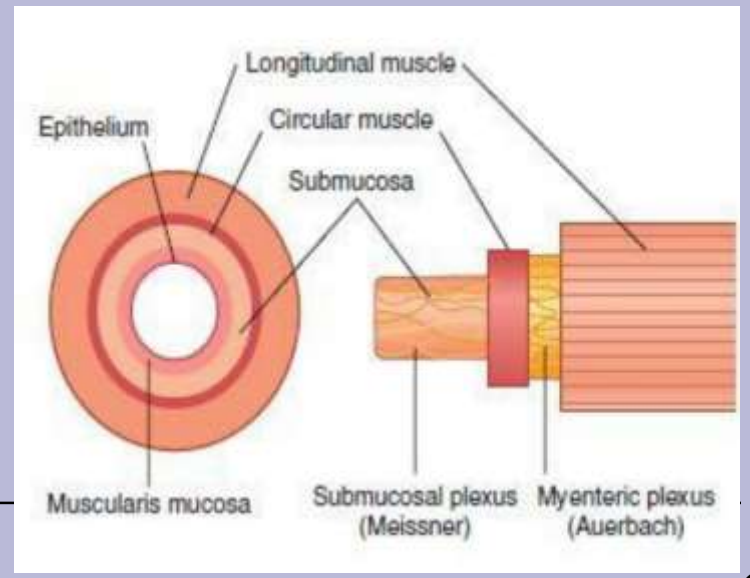
PROKINETIC DRUGS

LEARNING OBJECTIVES

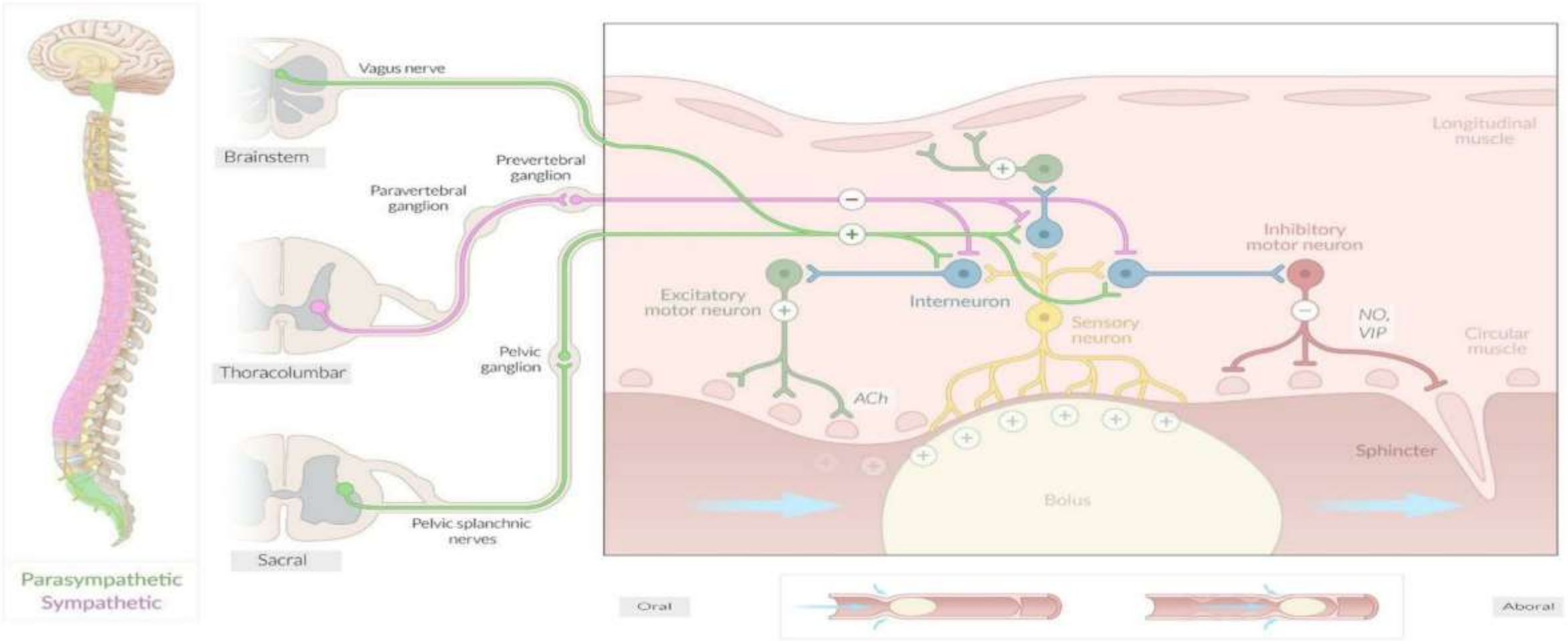
- Recall the physiology of gut motility
- Define pro-kinetics / pro-motility agents
- Classify pro-kinetics / pro-motility agents
- Discuss the mechanism of action of different pro-Kinetics
- Describe the main therapeutic indications and adverse effects of different pro-kinetics

CONTROL OF GUT MOTILITY





CONTROL OF GASTROINTESTINAL MOTILITY



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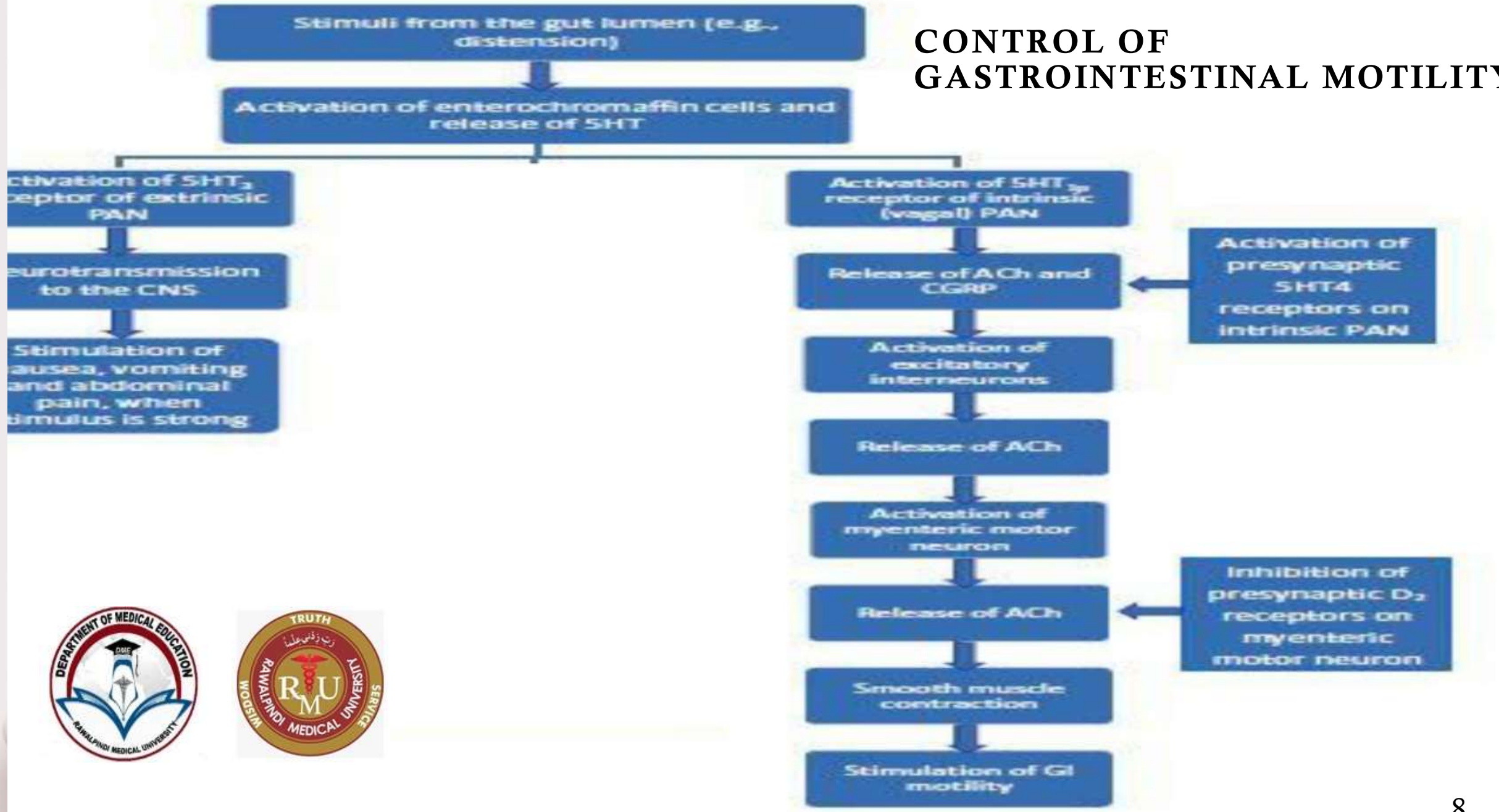


WHAT ARE PROKINETIC DRUGS?

CLASSIFICATION

DOPAMINE RECEPTOR ANTAGONIST

- Metoclopramide
- Domeperidone
- itopride

SEROTONIN RECEPTOR AGONIST

- Cesapride
- Tegaserod
- prucalopride

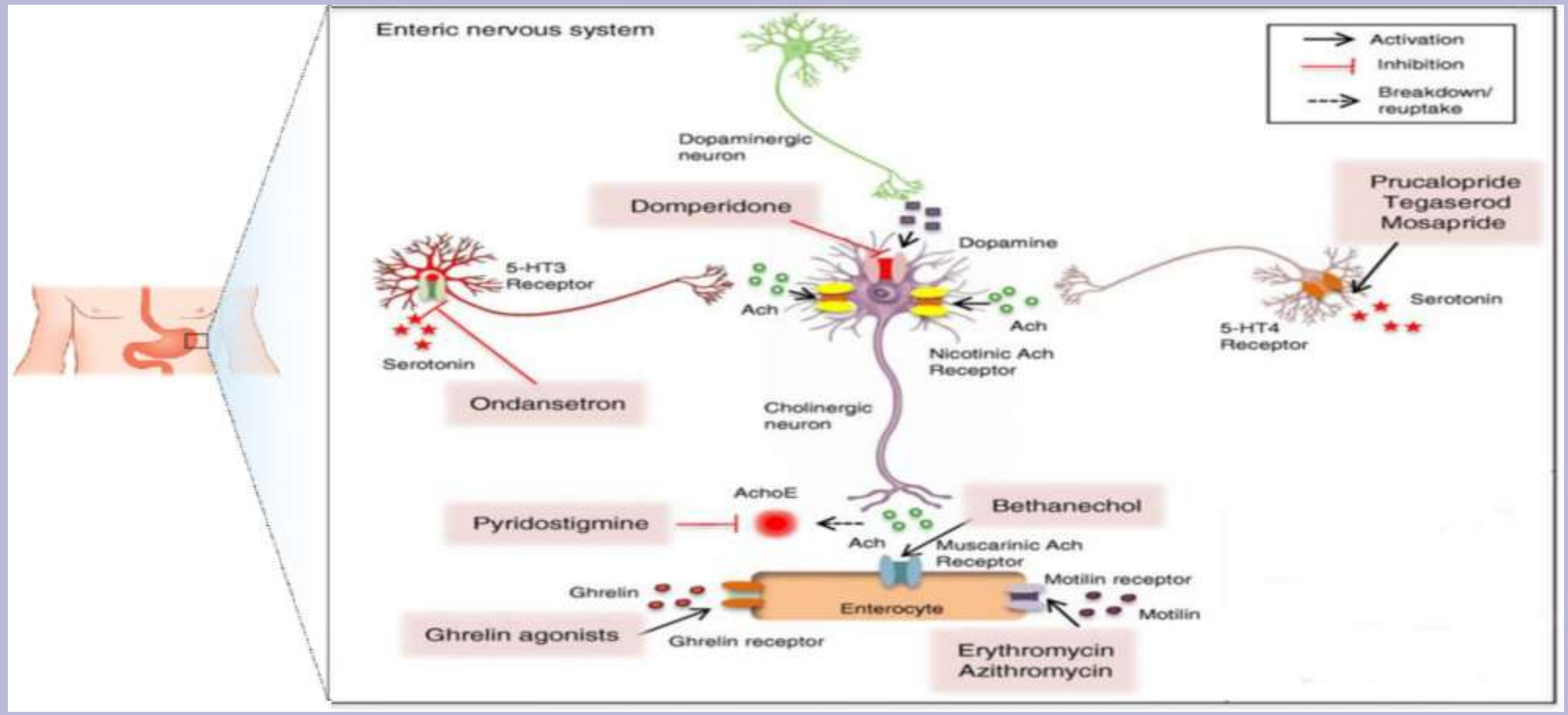
CHOLINOMIMETICS

- Bethanecol
- Pyridostigmine
- Neostigmine
- Acotiamide

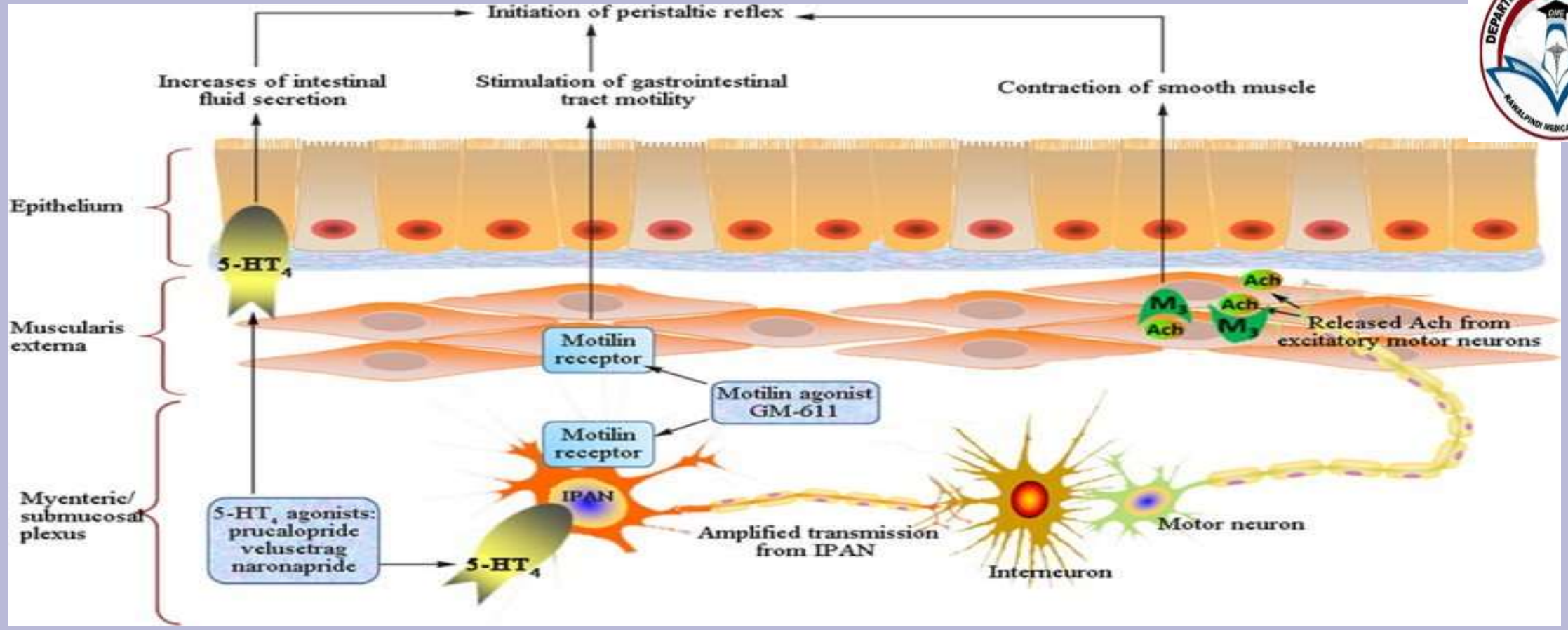
CLASSIFICATION

MOTILIN RECEPTOR AGONIST	CHOLECYSTOKININ RECEPTOR ANTAGONIST	GHERLIN AGONIST
Erythromycin	Sinaclide	Relamorelin
Azithromycin	loxiglumide	ulimorelin
camicinal		Others: opiod antagonist, leuprolide

MECHANISM OF ACTION OF PROKINETIC DRUGS

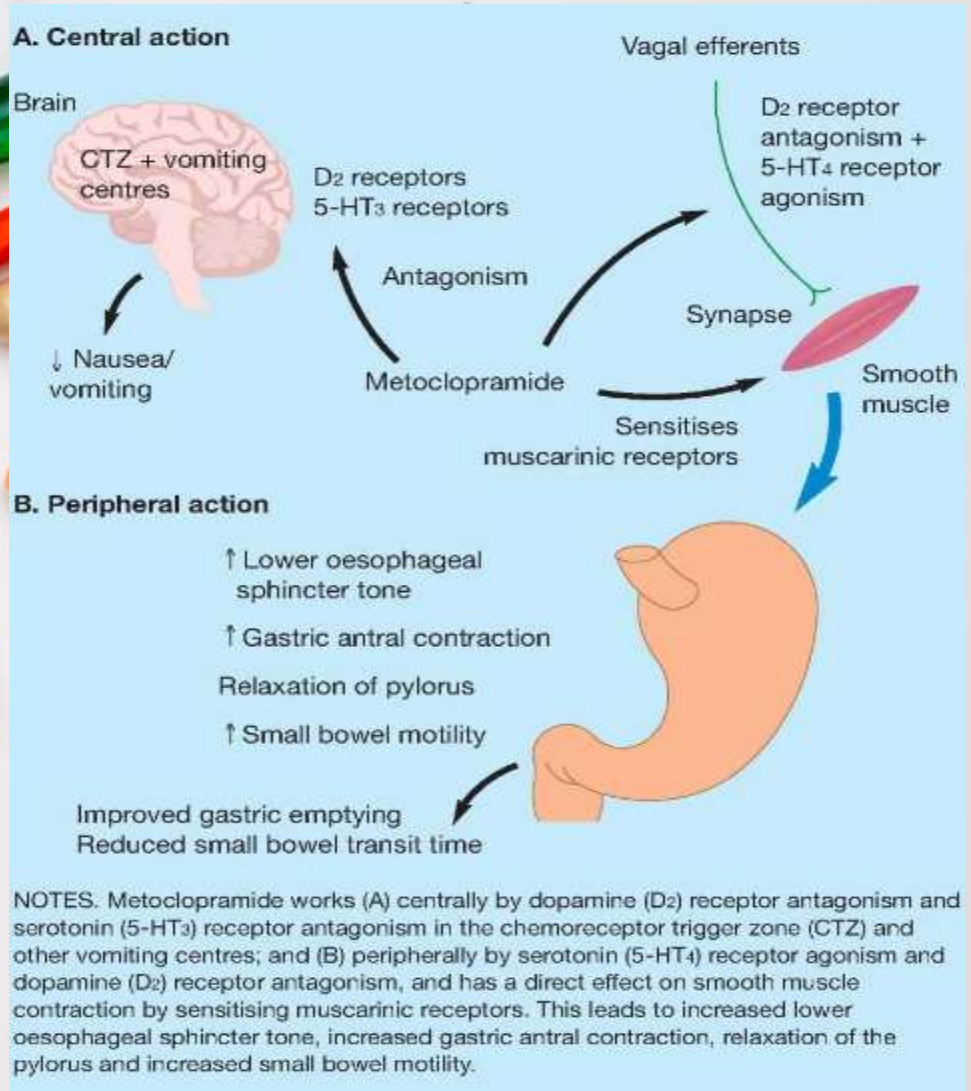


MECHANISM OF ACTION OF PROKINETIC DRUGS



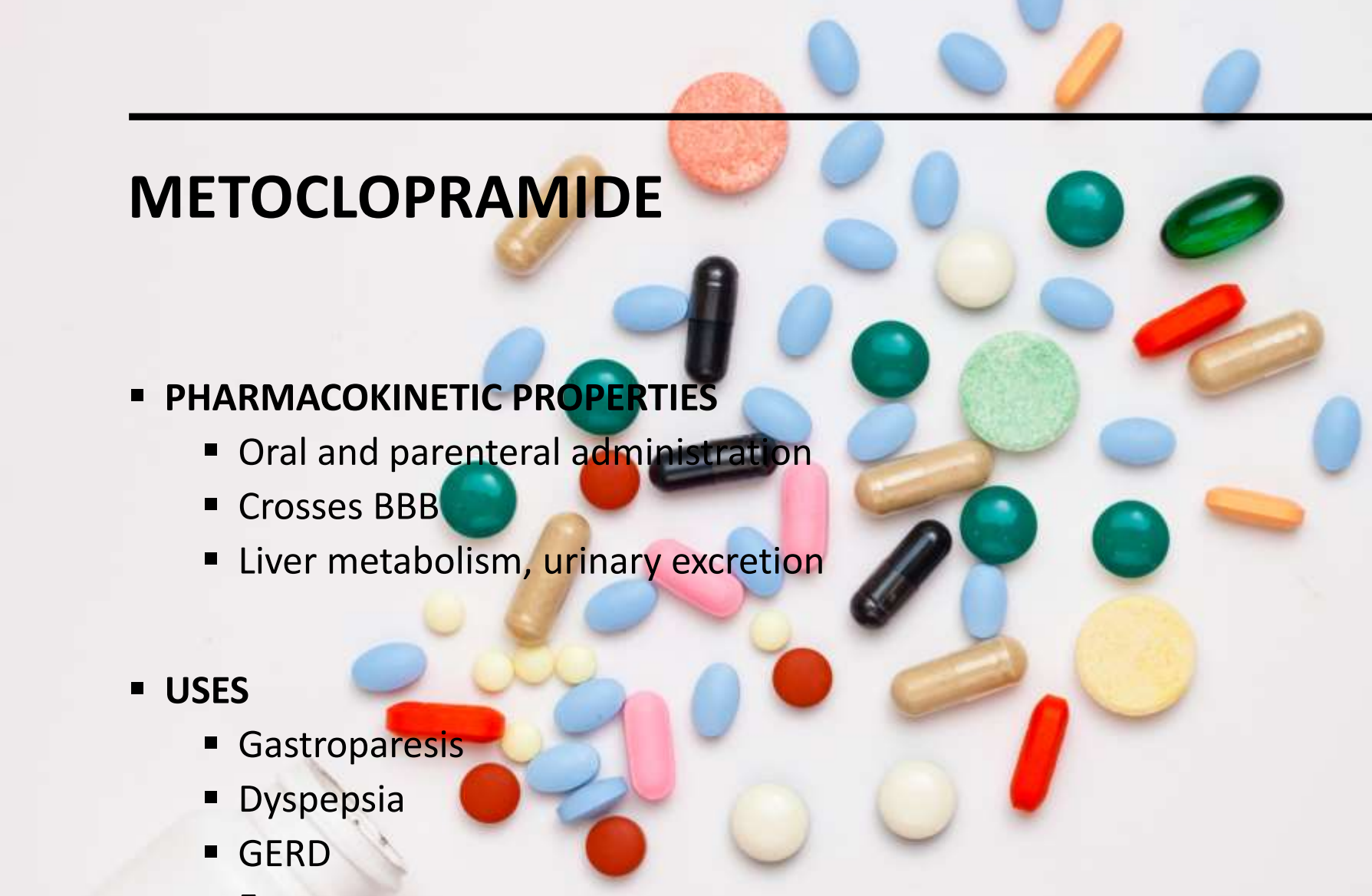
DOPAMINE RECEPTOR ANTAGONIST

- Metoclopramide promotes gut motility via
  - Inhibition of presynaptic and postsynaptic D2 receptors
  - Stimulation of presynaptic excitatory 5HT4 receptors
  - Weak inhibition of 5HT3 receptors



NOTES. Metoclopramide works (A) centrally by dopamine (D_2) receptor antagonism and serotonin ($5\text{-}HT_3$) receptor antagonism in the chemoreceptor trigger zone (CTZ) and other vomiting centres; and (B) peripherally by serotonin ($5\text{-}HT_4$) receptor agonism and dopamine (D_2) receptor antagonism, and has a direct effect on smooth muscle contraction by sensitising muscarinic receptors. This leads to increased lower oesophageal sphincter tone, increased gastric antral contraction, relaxation of the pylorus and increased small bowel motility.

METOCLOPRAMIDE



- **PHARMACOKINETIC PROPERTIES**
  - Oral and parenteral administration
  - Crosses BBB
  - Liver metabolism, urinary excretion

- **USES**
  - Gastroparesis
  - Dyspepsia
  - GERD
  - Emergency surgery

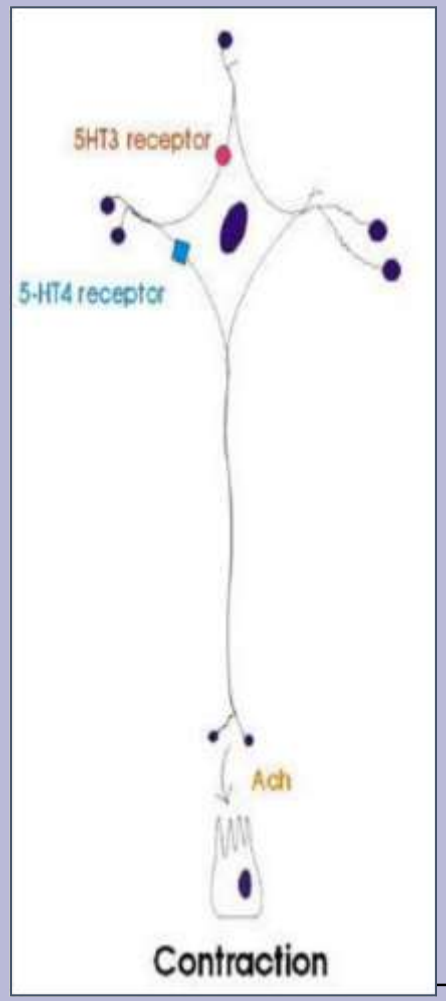
METOCLOPRAMIDE

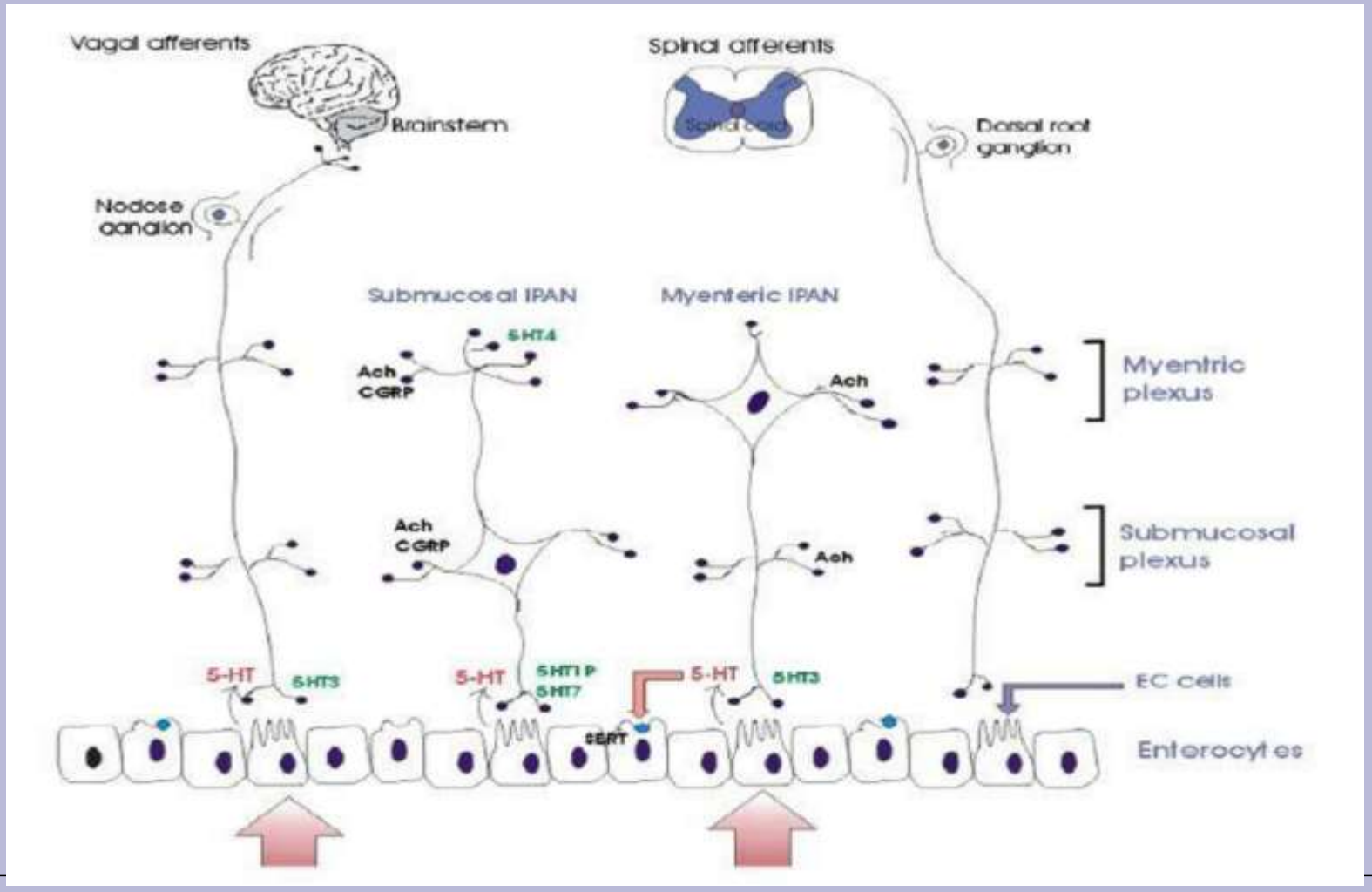
- **ADVERSE EFFECTS**
  - EPS CNS effects
  - Endocrine: galactorrhea
  - Reproductive: gynecomastia
    Menstrual abnormalities

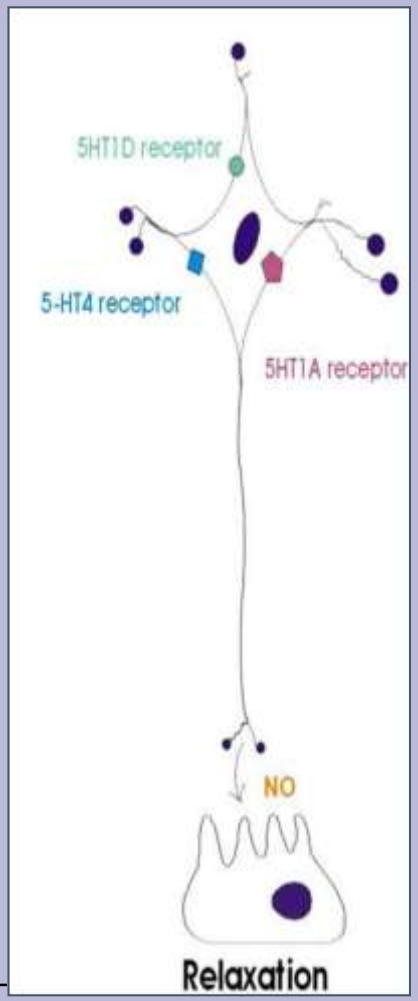
SEROTONIN RECEPTOR AGONIST

	5HT1	5HT3	5HT4
RECEPTOR DISTRIBUTION	Enteric neurons	Enteric neurons Central and peripheral nervous system	Enteric neurons Enterocytes CNS
FUNCTIONAL EFFECTS	Decrease NT release	Increase NT release Increase secretion activates IPANs	Increase NT release Increase secretion activates IPANs Relaxes smooth muscles Inhibits 5HT release from EC cells

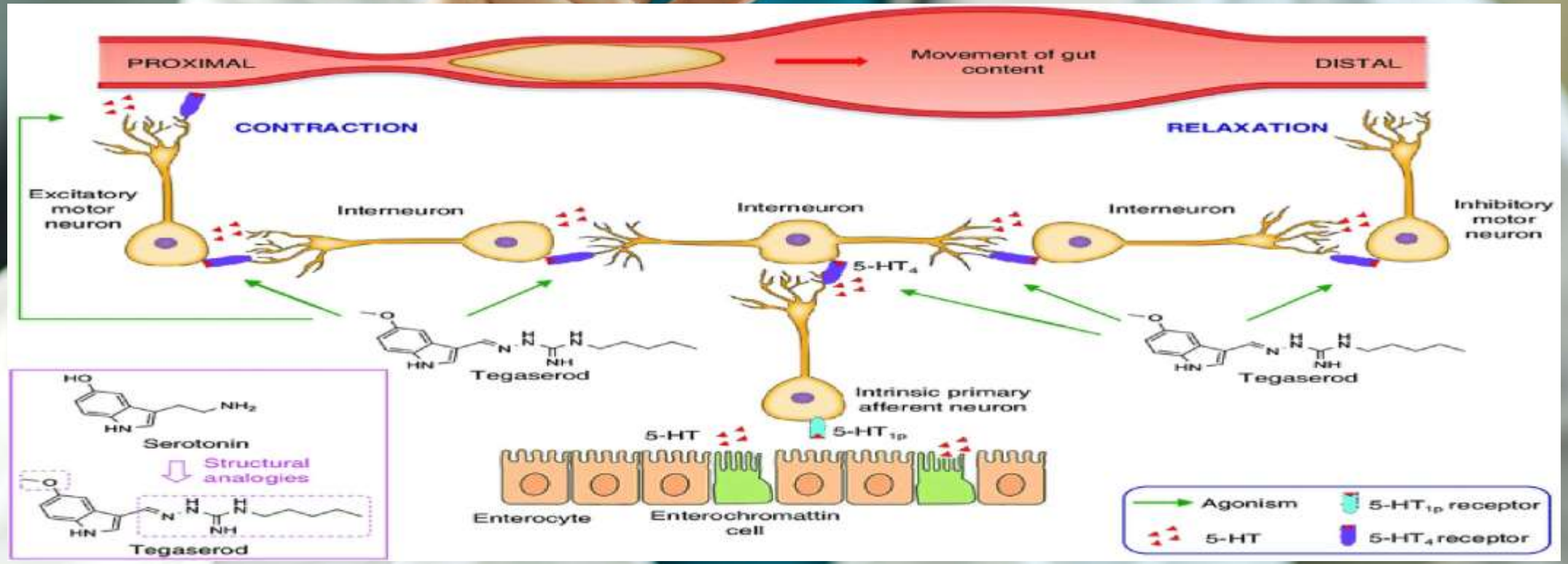
SEROTONIN RECEPTOR AGONIST





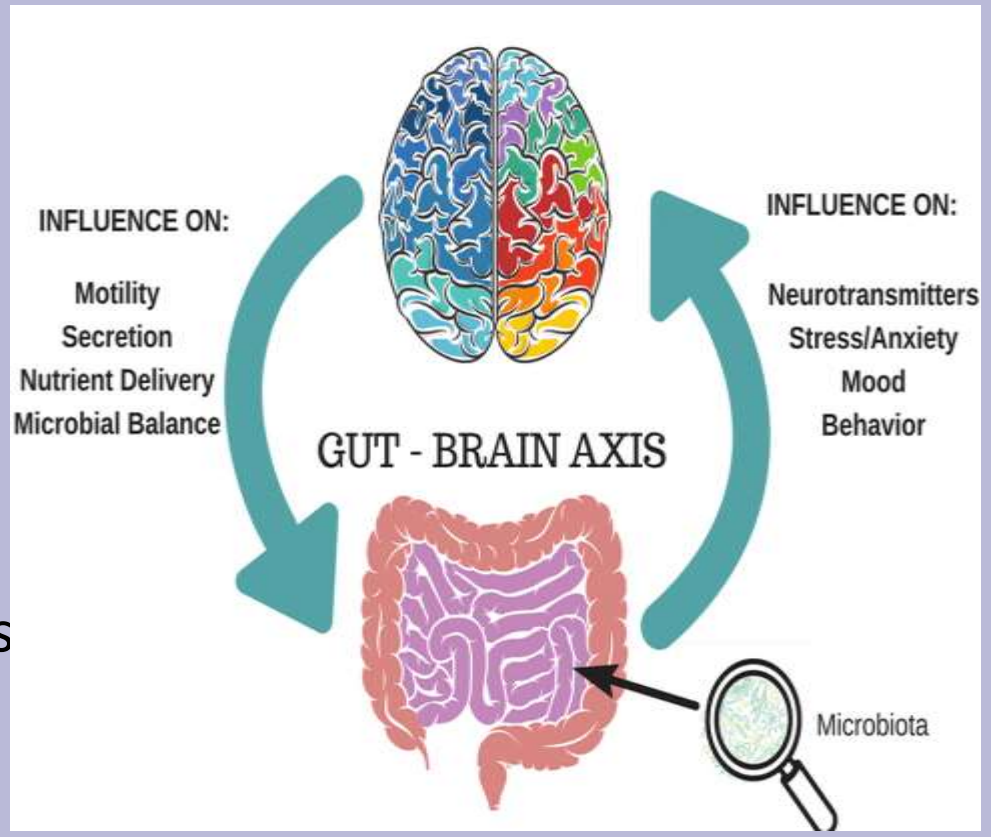


SEROTONIN RECEPTOR AGONIST MECHANISM OF ACTION



SEROTONIN RECEPTOR AGONIST

- **GIT EFFECTS**
- Improves tone of LES
- Increase esophageal peristalsis
- Improves antroduodenal co-ordination
- Accelerates gastric emptying
- Increase colonic activity and fluid secretions
- Mild anti-emetic activity



SEROTONIN RECEPTORS AGONIST

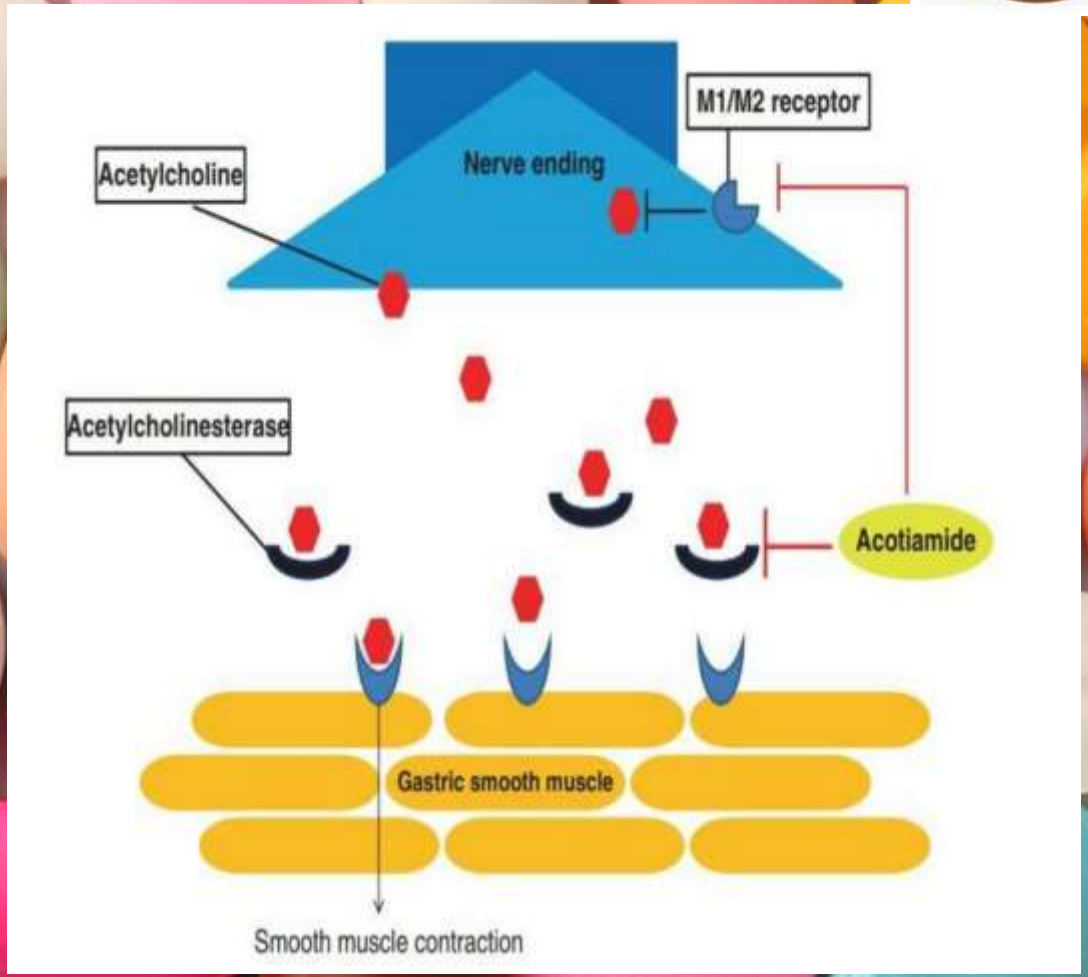
- **ADVERSE EFFECTS**
  - Nausea
  - Diarrhea
  - Abdominal pain
  - QT prolongation

CHOLINOMIMETICS

Do not fulfill the true definition of prokinetics

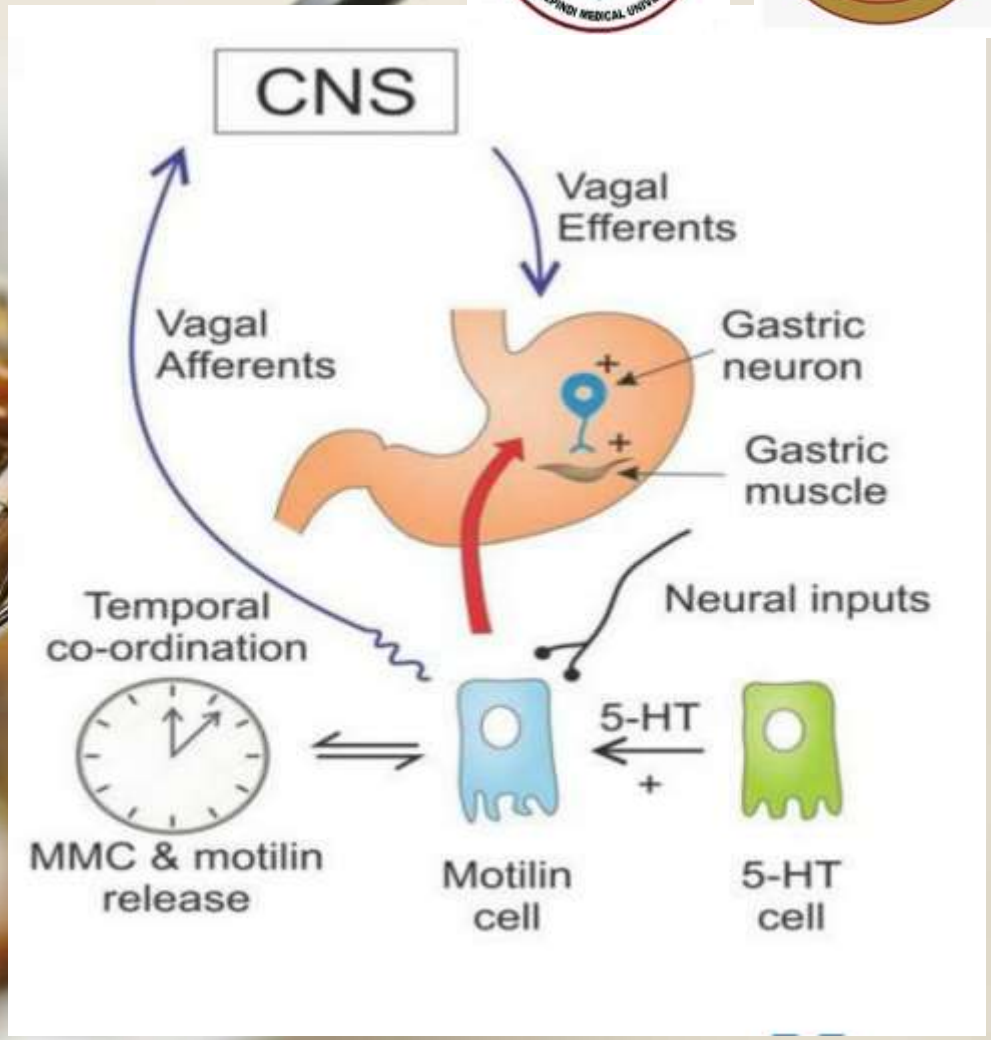
Effect	Bethanechol	Prokinetics
Muscle tone	↑	↑
Peristalsis	↑	↑↑
Antroduodenal coordination	0	↑↑
Gastric emptying	↑	↑↑
Antagonism by antimuscarinics	Yes	Yes

↑ = Increase.



MOTILIN RECEPTOR AGONISTS

- Motilin is endogenous peptide
- produced by EC cells of duodenum
- Motilin receptors are found within
  - Cholinergic nerves within enteric nervous system
  - Gastric smooth muscle cells
- Motilinomimetics
  - Motilides
  - Motilin analogues



GHRELIN RECEPTOR AGONIST

- Ghrelin is an appetite stimulating peptide.
- Releases from endocrine cells in oxyntic glands of fundus and corpus.
- Binds to recpetors in GIT and brain
- Exogenous synthetic ghrelin increase gastric emptying
- Ramorelin is synthetic and more stable with long plasma half life
- SC injection: 6 times more potent than natural
- **ADVERS EEFFECTS:**
- Dizziness, fatigue, abdominal pain/cramping
- decreased blood pressure, hunger, feeling cold, muscular weakness

CHOLECYSTOKININ RECEPTOR ANTAGONIST

- It's a hormone produced throughout GIT espescially duodenum and jejunum
- Produces its physiologic effects via GPCR, CCK1 and CCK2 receptors throughout the GIT
- CCK1R antagonist block the effect of endogenous cholecystokinin and increase gastric and colonic motility

THERAPEUTIC USES OF PROKINETIC DRUGS

- **Upper Gastrointestinal tract**
- Diabetic Gastroparesis
- Post operative nausea and vomiting
- GERD
- Functional dyspepsia
- Intestinal manifestations of systemic disease (scleroderma, amyloidosis)
- **Lower Gastrointestinal tract**
- Chronic pseudo –obstruction
- Post operative ileus
- Irritable bowel syndrome
- Constipation

HOW TO ACCESS DIGITAL LIBRARY

- Go to the website of HEC National Digital Library.
- On Home Page, click on the INSTITUTES.
- A page will appear showing the universities from Public and Private Sector and other Institutes which have access to HEC National Digital Library HNDL.
- Select your desired Institute.
- A page will appear showing the resources of the institution
- Journals and Researches will appear
- You can find a Journal by clicking on JOURNALS AND DATABASE and enter a keyword to search for your desired journal.

FURTHER READING

- Tack J, Goelen N, Carbone F, Van den Houte K, Masuy I, Wauters L, Basnayake C, Talley N, Pauwels A, Vanuytsel T, Janssen P. Prokinetic effects and symptom relief in the pharmacotherapy of gastroparesis. Gastroenterology. 2020 May 1;158(6):1841-2.
- Usai-Satta P, Lai M, Oppia F, Cabras F. Effects of Prokinetics on the Digestive Tract. Current Reviews in Clinical and Experimental Pharmacology (Formerly Current Clinical Pharmacology. 2022 Nov 1;17(3):161-5.

END OF LECTURE ASSESSMENT

1.Metoclopramide produces its prokinetic effect by mainly acting on which of the following receptor?

a) D1 receptor
b) 5HT4 receptor
c) 5HT1 receptor
d) Motilin receptor
e) CCK- receptor

2.Which prokinetic agent is a macrolide antibiotic and acts by stimulating motilin receptors in the gastrointestinal tract?

a) Erythromycin

b) Metoclopramide

c) Tegaserod

d) Domperidone

END OF LECTURE ASSESSMENT

3. Which of the following is not a neuropeptide/neurotransmitter involved in gas trointestinal motility?

a) Motilin
b) Ghrelin
c) CCK
d) Acetylcholine
e) Glutamate

THANK YOU