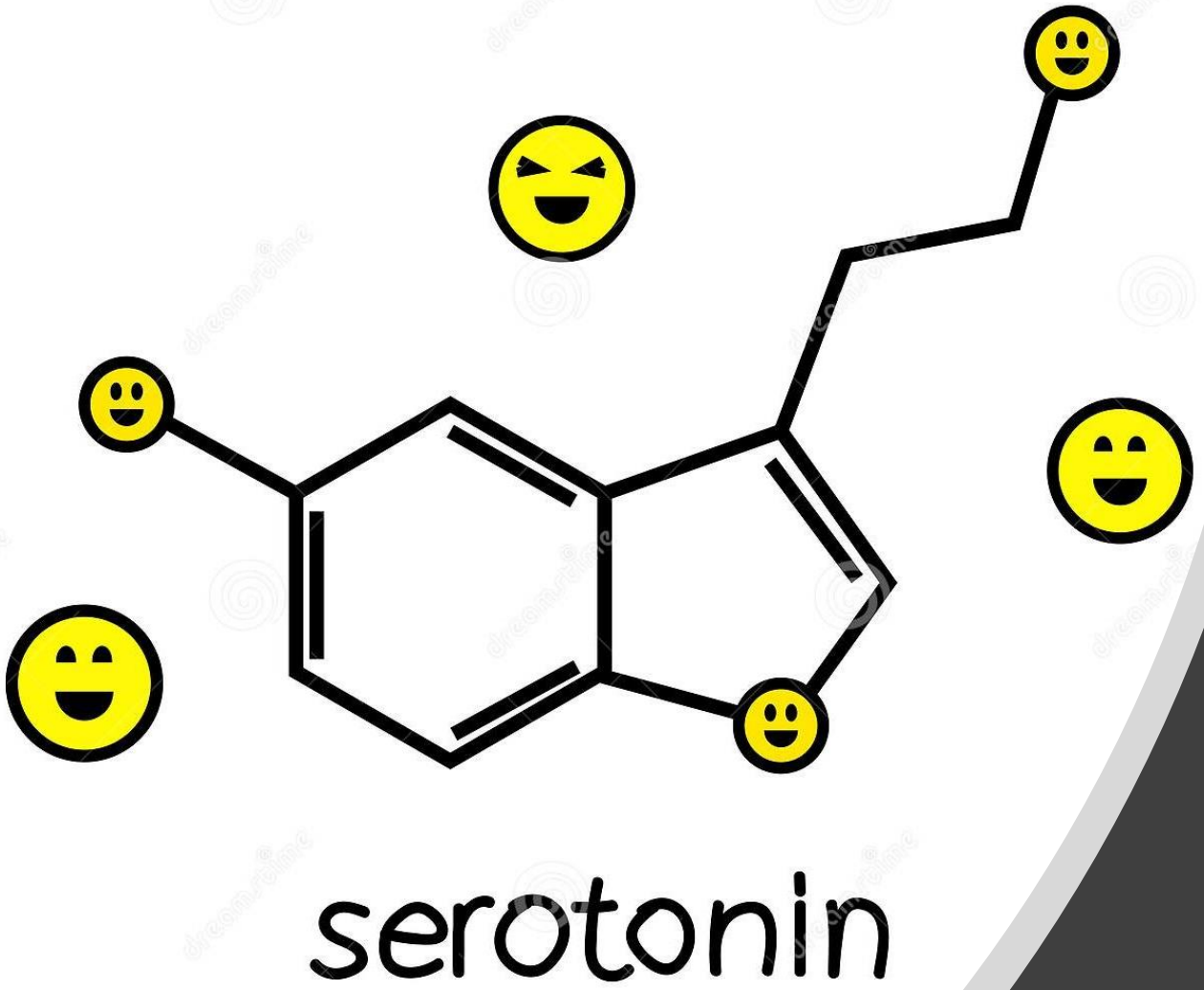




# Dr. Sidrah Ghafoor

**KHYBER GIRLS MEDICAL COLLEGE**


**Infection and inflamation module**

**Year**

# LEARNING OBJECTIVES

By the end of the session, the students shall be able to

- Enlist serotonin agonists
- Classify serotonin antagonists
- Describe the mechanism of action of serotonin
- Describe the organ system effects of serotonin
- Describe the clinical uses of serotonin agonists and antagonists
- Describe the pharmacological basis of Ondansetron in chemotherapy induced nausea and vomiting

Autacoids are biological factors which act like local hormones, have a brief duration, and act near their site of synthesis

# AUTOCOIDS

## AMINE DERIVED

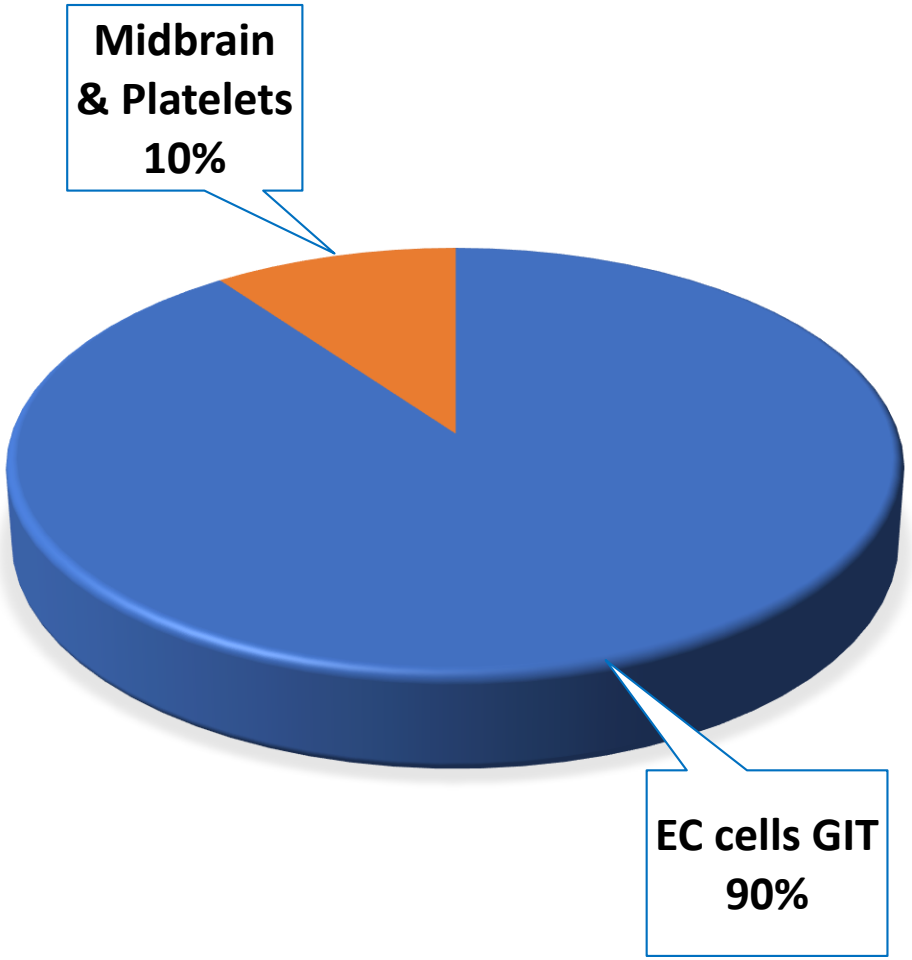
Histamine
Serotonin

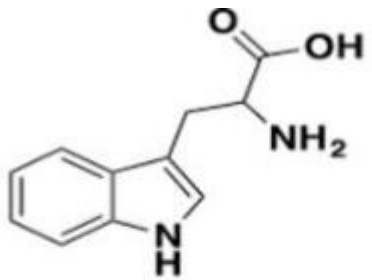
## PEPTIDE DRIVED

Angiotensin
Bradykinin

## LIPID DERIVED

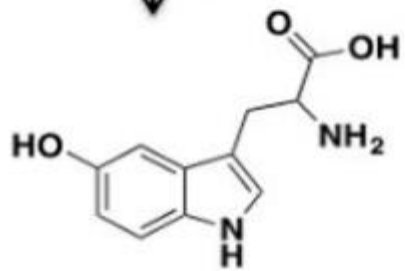
Prostaglandin
Leukotrienes



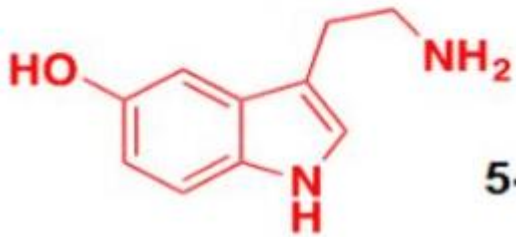

L-Tryptophan

*Tryptophan hydroxylase (TPH)*




5-Hydroxy-L-Tryptophan
(5HTP)

*Aromatic L-amino acid decarboxylase*




**Serotonin**
5-Hydroxytryptamine (5-HT)

**CNS**
Sleep, Feeding,

All serotonin receptors are G-protein coupled which affect cAMP or IP3 levels except 5-HT3 receptors which are ligand gated Na-K ion channels

- Stabilizes mood
- Inhibit pain pathway
- Regulate sleep

## CNS

- Increase secretions & contractility
- Nausea & vomiting

## GIT

- Vasoconstriction / vasodilation
- Platelet aggregation

## VESSELS

- Positive ionotropic and chronotropic effect

## HEART

- Bronchoconstriction
- Stimulation of respiration / hyperventilation

## RESP

- Decrease appetite
- Metabolic rate
- Temperature regulation

## ENDO

# SEROTONIN RECEPTOR AGONISTS

| 5-HT1A | 5-HT1B/D | 5-HT4 |
| --- | --- | --- |
| • Buspirone | • Sumatriptan<br>• Zolmitriptan<br>• Rizatriptan<br>• Elepriptan<br>• Almotriptan<br>• Naratriptan<br>• Frovatriptan | • Metoclopramide<br>• Domperidone<br>• Cisapride |

# BUSPIRONE

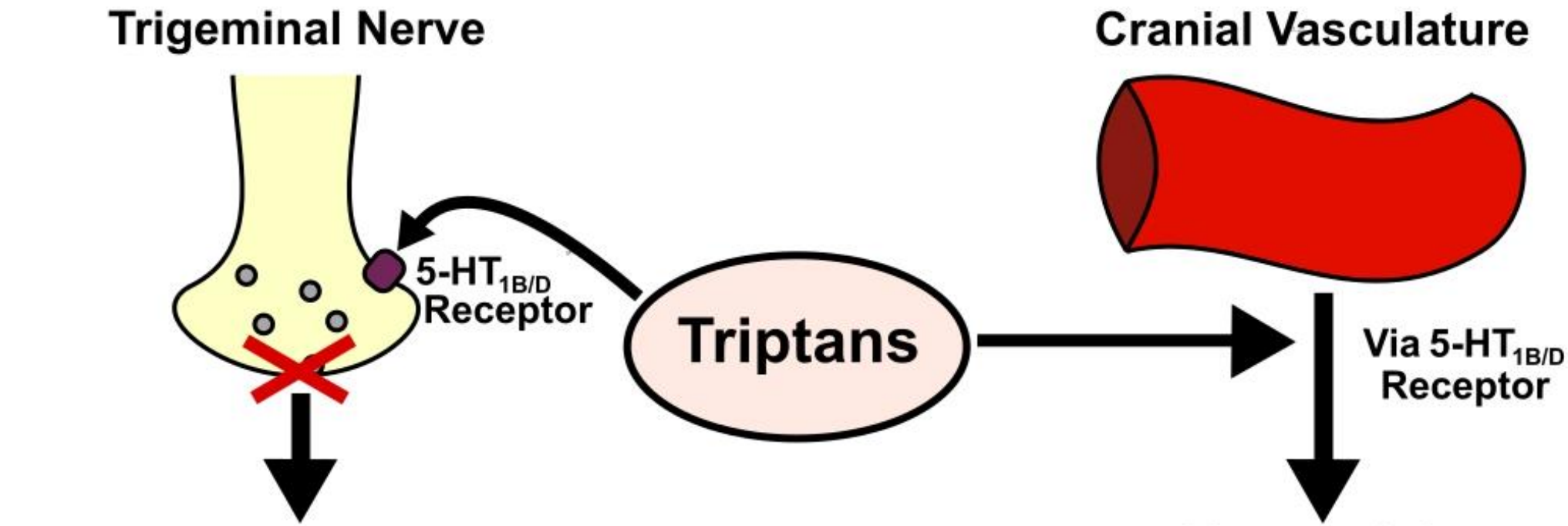
- 5-$HT_{1A}$ receptor agonist
- Indicated for treatment of anxiety disorders
- Unlike many drugs used to treat anxiety, buspirone does not exhibit sedative or hypnotic properties.
- Side effects include dizziness, headaches, nausea, nervousness, and paresthesia

# TRIPTANS

- Selective agonists of 5-HT1B/1D receptors in blood vessels and nerve endings in the brain
- Indicated for treatment of acute attacks of migraine
- All triptans can be given orally; Sumatriptan and Zolmitriptan have nasal preparations while Sumatriptan can also be given subcutaneously.

# TRIPTANS

- Triptans have at least three modes of action.
  - **Vasoconstriction** of pain producing intra cranial extracerebral vessels by a direct effect on vascular smooth muscle.
  - **Inhibition of vasoactive neuropeptide release** by trigeminal terminals innervating intracranial vessels and the dura mater.
  - **Inhibition of nociceptive neurotransmission** within the trigeminocervical complex in the brainstem and upper cervical spinal column.


Trigeminal Nerve
Cranial Vasculature
5-HT1B/D Receptor
Triptans
Via 5-HT1B/D Receptor
Prevents peptide release that would lead to:
- Vasodilation
- Neurogenic inflammation
- Pain
Vasoconstriction

# TRIPTANS

- **Adverse effects:** Flushing, dizziness, paresthesia, chest tightness, rise in blood pressure and coronary vasospasm.

- **Contraindications:** Pregnancy, Ischemic heart disease, peripheral vascular disease, uncontrolled hypertension.

- Triptans shall not be administered along with and within 24 hours of taking ergot alkaloid.

# METOCLOPRAMIDE

- Metoclopramide has both central and peripheral actions
- Antagonistic action at D2 receptors in chemoreceptor trigger zone; also blocks 5-HT3 receptors in CTZ at higher doses
- It increases gastric motility due to agonistic action on 5-HT4 receptors and antagonistic effect on D2 receptors in stomach

# METOCLOPRAMIDE

- **Clinical uses** include treatment of nausea, gastroesophageal reflex disease and gastroparesis

- **Common side effects** include movement disorders (restlessness, dystonia), hypotension and galactorrhea

- **Contraindications** include Parkinson disease, epilepsy, depressive illness and mechanical bowel obstruction

# SEROTONIN RECEPTOR ANTAGONISTS

| 5-HT1 | 5-HT2 | 5-HT3 |
| --- | --- | --- |
| • Ergot Alkaloids | • Cyproheptadine<br>• Methysergide<br>• Atypical antipsychotics<br>• Ketanserin | • Ondansetron<br>• Granisetron |

# ERGOT ALKALOIDS

- Antagonistic actions on 5-HT1 receptors, and also have affinity for alpha-receptors and dopamine receptors

- Used in the treatment of acute migraine attacks as they cause vasoconstriction by binding to 5-HT1 receptors on intracranial vessels

- Ergotamine is available in oral, sublingual and suppository form. Dihydroergotamine can be used IM, SC and orally.

# ERGOT ALKALOIDS

- **Adverse effects:** Nausea, vomiting, dependence, and rebound headaches

- **Contraindicated** in patients with uncontrolled hypertension, ischemic heart disease, peripheral vascular disease and renal failure.

# CYPROHEPTADINE

- 5-HT2A receptor with additional antihistaminic & anticholinergic effects.

- Used as off-label treatment for serotonin syndrome, carcinoid syndrome, post gastrectomy dumping syndrome, prophylaxis of migraine, and for increasing appetite.

- Common adverse effects include dry mouth, dizziness and weight gain.

# METHYSERGIDE

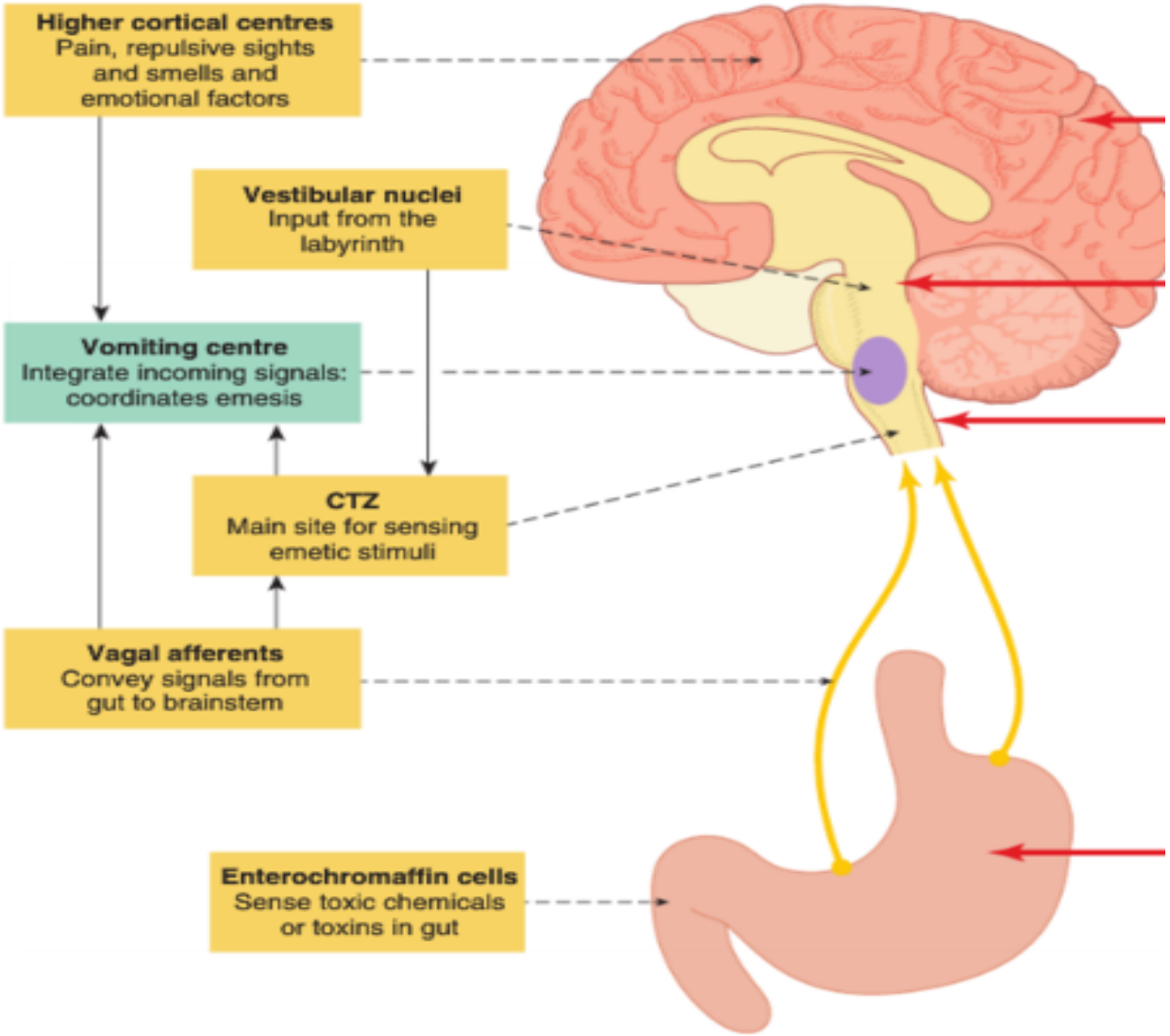
- 5-HT2 receptor antagonist
- Uses include as a prophylactic agent for migraine and cluster headaches, and as treatment option in serotonin syndrome and carcinoid syndrome.
- Long term use can result in pulmonary and retroperitoneal fibrosis.

# ATYPICAL ANTIPSYCHOTICS

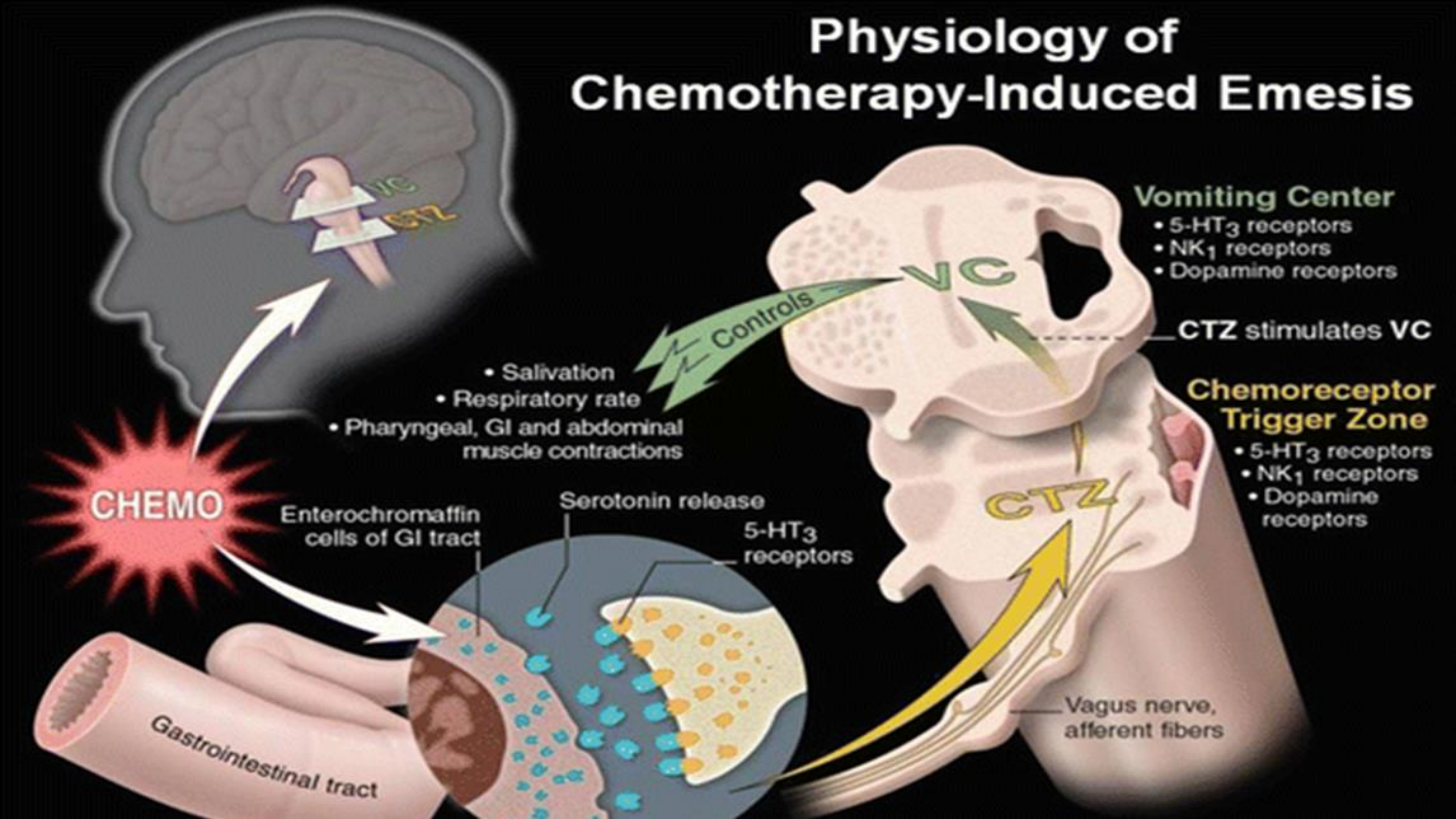
- Olanzapine, clozapine, risperidone and quetiapine are 5-HT2 antagonist in addition to being dopamine receptor antagonists.

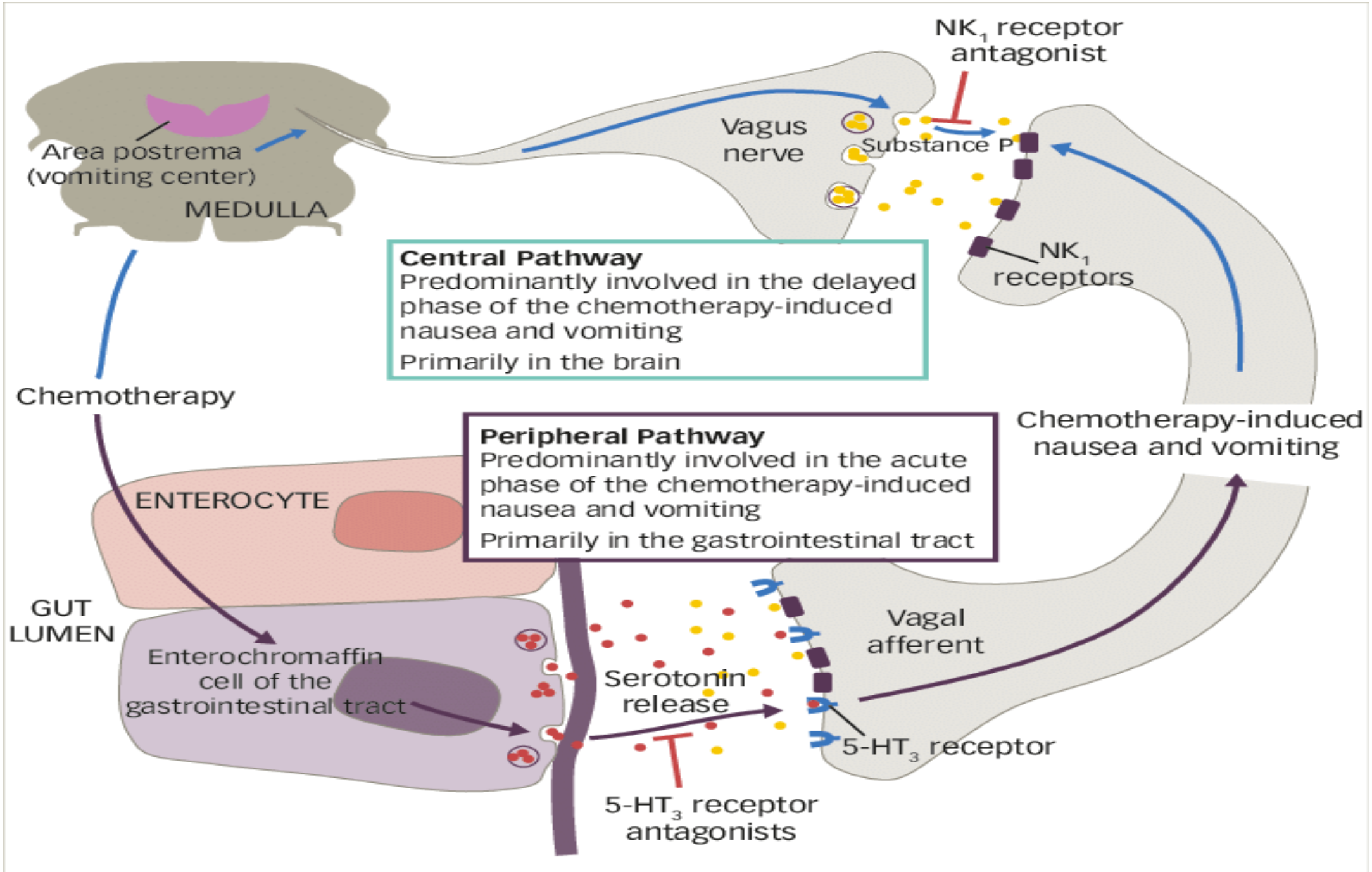
- They are used in the treatment of schizophrenia, and bipolar disorders.

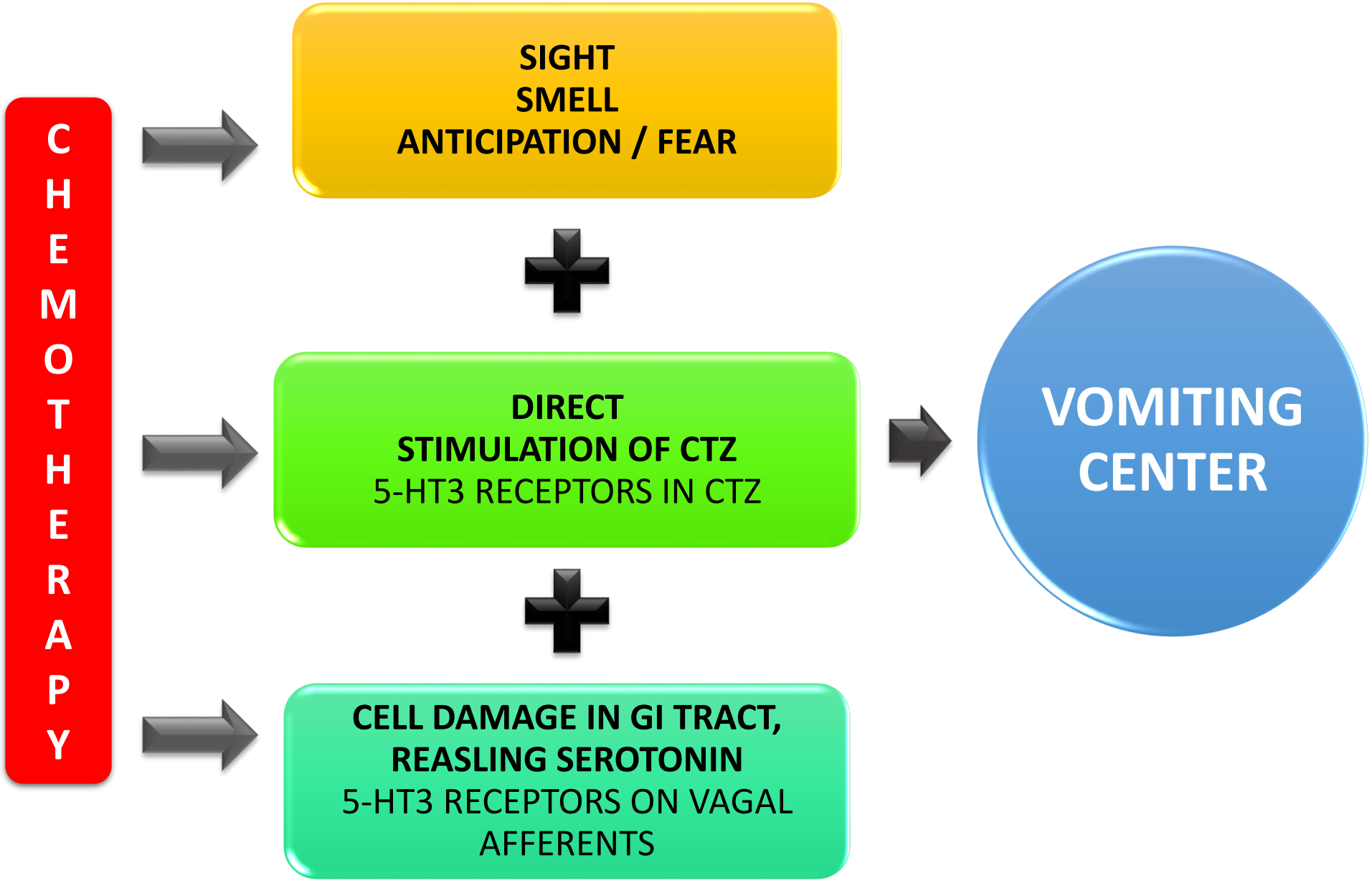
# NAUSEA & VOMITING, AND SEROTONIN



# Physiology of Chemotherapy-Induced Emesis




NK1 receptor antagonist
Area postrema (vomiting center)
MEDULLA
Vagus nerve
Substance P
NK1 receptors
Central Pathway
Predominantly involved in the delayed phase of the chemotherapy-induced nausea and vomiting
Primarily in the brain
Chemotherapy
Chemotherapy-induced nausea and vomiting
Peripheral Pathway
Predominantly involved in the acute phase of the chemotherapy-induced nausea and vomiting
Primarily in the gastrointestinal tract
ENTEROCYTE
GUT LUMEN
Enterochromaffin cell of the gastrointestinal tract
Serotonin release
Vagal afferent
5-HT3 receptor
5-HT3 receptor antagonists


CHEMOTHERAPY
SIGHT
SMELL
ANTICIPATION / FEAR
DIRECT
STIMULATION OF CTZ
5-HT3 RECEPTORS IN CTZ
CELL DAMAGE IN GI TRACT,
REASLING SEROTONIN
5-HT3 RECEPTORS ON VAGAL
AFFERENTS
VOMITING
CENTER

# 5-HT3 RECEPTOR ANTAGONISTS

- Ondansetron, Granisetron, Polanosetron & Dolasetron
- Act by blocking 5-HT3 receptors on vagal afferent nerve fibers and in the chemoreceptor trigger zone (CTZ) in medulla
- Indicated for chemotherapy induced-, and post-operative nausea and vomiting
- QT prolongation seen with high doses of Ondansetron and Dolasetron

# SEROTONIN SYNDROME

- A toxic state with autonomic, motor and mental status changes caused by excessive serotonin activity

- Most often a result of concomitant or consecutive treatment with selective serotonin reuptake inhibitors (SSRIs), Tricyclic antidepressants (TCAs), Monoamine oxidase inhibitors (MAOi) or Tryptophan

**Mental status changes**

Agitation

Pressured speech

**Autonomic instability**

Tachycardia

Diarrhea

Shivering

Diaphoresis

Mydriasis

**Neuromuscular abnormalities**

Clonus

Hyperreflexia (lower > upper)

Tremor

Seizure

# SEROTONIN SYNDROME

- Management involves supportive care including
  - Hydration
  - Cooling
  - Benzodiazepines for agitation

- Specific therapy is Cyproheptadine which antagonizes the action of excessive serotonin

# Thanks !!