Antiemetics

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Learning objectives

- Classify the main different classes of antiemetic drugs according to their mechanism of action.
- Know the characteristic pharmacokinetics & dynamics of different classes of antiemetic drugs.
- Identify the selective drugs that can be used according to the cause of vomiting.
- Learn the adjuvant antiemetics.
- Describe the major side effects for the different classes of antiemetics.

Vomiting

- **is forceful expulsion of gastric contents through the mouth.**
- **Can vomiting be considered as a disease?**
- **It is a manifestation of many conditions and diseases.**

Consequences of vomiting

Severe vomiting may result in :

- **Dehydration**
- **Acid-base imbalance**
- **Electrolyte depletion**
- **Aspiration, pneumonia**

How is vomiting induced?

Vomiting center respond to inputs from:

- Higher cortical centers stimulation (CNS)
- Disturbance of vestibular system
- Chemoreceptor trigger zone (CTZ) stimulation
- The periphery (Pharynx, GIT) via sensory nerves.

Vomiting center can be stimulated by the following:

1. Higher cortical centers stimulation:

- ✓ Emotional factors
- ✓ Nauseating smells or sights

2. Disturbance of vestibular system:

- ✓ Motion sickness (H1 & M1 receptors)

3. The periphery via sensory nerves

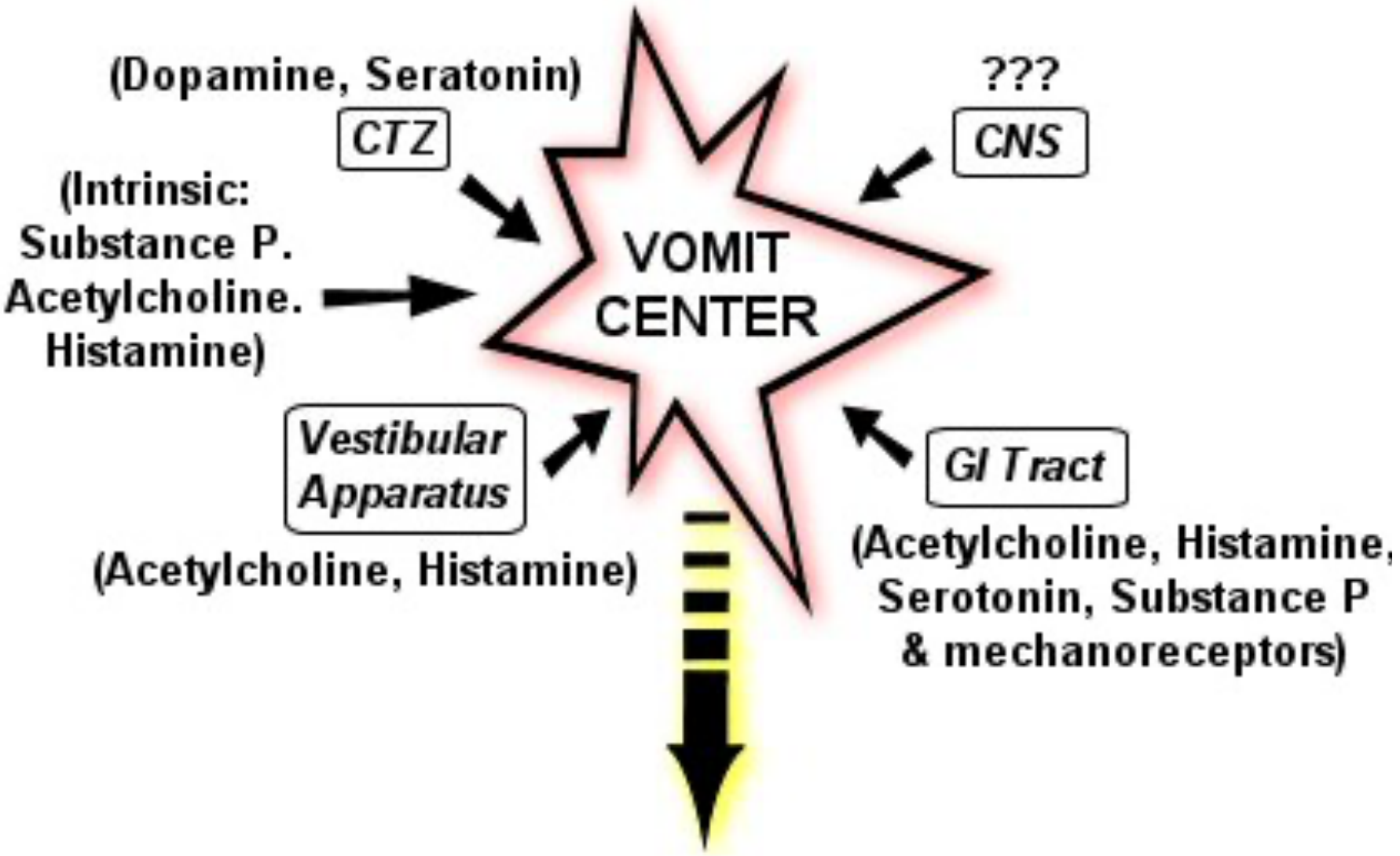
- ✓ GIT irritation
- ✓ Myocardial infarction
- ✓ Renal or biliay stones

4. Stimulation of chemoreceptor trigger zone (CTZ)

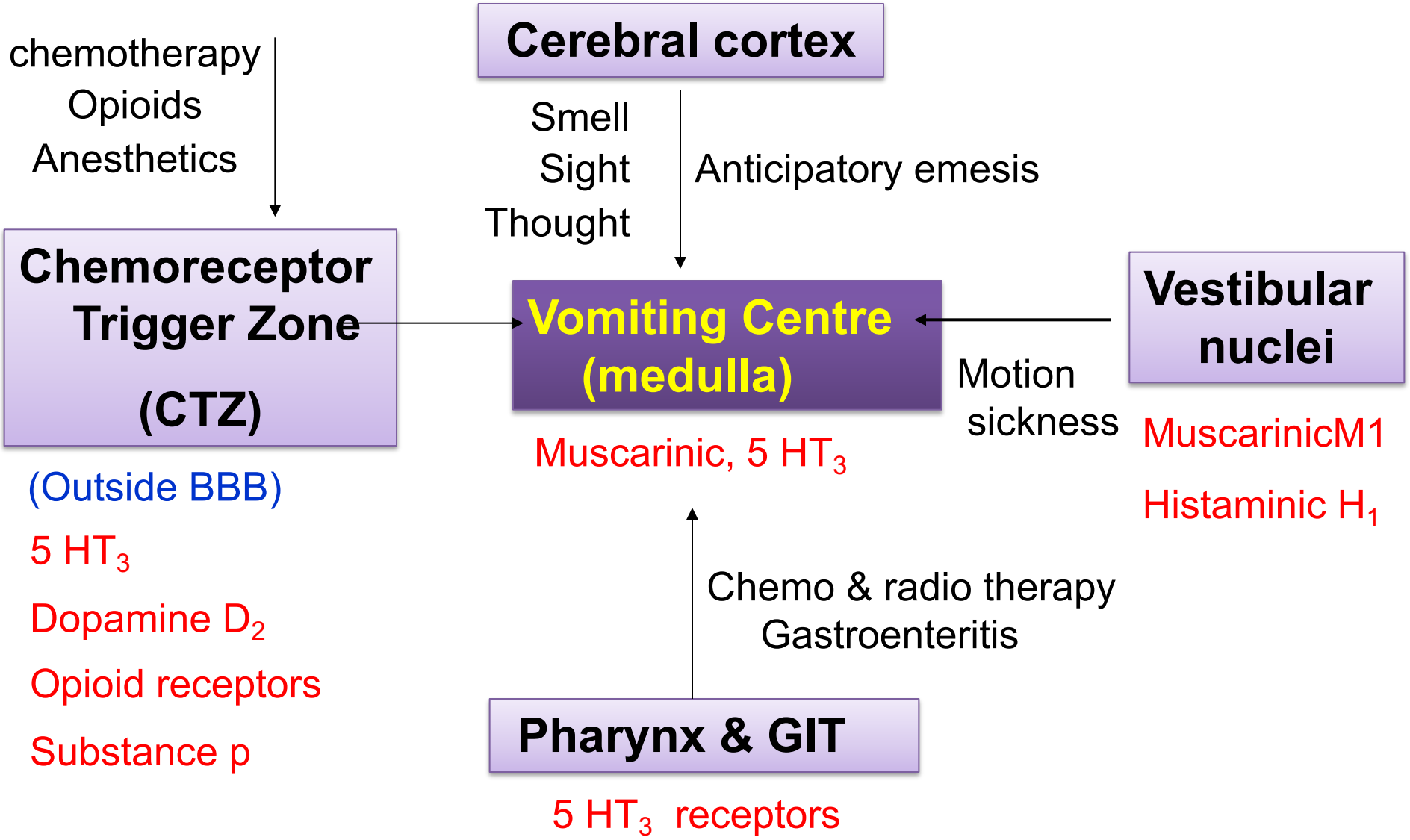
- CTZ is an area of medulla that communicate with vomiting center to initiate vomiting.
- CTZ is physiologically outside BBB.
- CTZ contains D_2 receptors, 5 HT_3 receptors & opioid receptors.
- **stimulated by:**

✓ Emetogenic drugs (opioids, general anesthetics, digitalis, L-dopa).
✓ chemicals and toxins (blood, CSF).
✓ Radiation.
✓ Uremia

Receptors Associated with Nausea and Vomiting



Pathophysiology of Emesis



Chemical transmitters & receptors involved in vomiting include:

- **Ach (Muscarinic receptors)**
- **Dopamine (D2)**
- **Histamine (Histaminergic receptors H1)**
- **Serotonin (5 -HT3)**
- **Substance P (Neurokinin receptors, NK1)**
- **Opioid (Opioid receptors)**

Classification of Antiemetic Drugs

1. 5-HT3 antagonists
2. D_2 receptor antagonists
3. NK_1 antagonists
4. H_1-receptor antagonists
5. Muscarinic receptor antagonists
6. Cannabinoids
7. Glucocorticoids

Serotonin (5-HT3) antagonists

- **Drugs as**
  - Ondansetron
  - Granisetron
- Orally or parenterally,
- have long duration of action, first pass effect
- The most potent antiemetic drugs
- Act by blocking 5-HT3 receptor centrally (in vomiting center, CTZ) and peripherally (5HT3 receptors on GI vagal afferents).

Uses of 5-HT3 antagonists

- **First choice for prevention of moderate to severe emesis:**
  - **Chemotherapy-induced nausea and vomiting (CINV) especially cisplatin**
  - **Post-radiation NV& Post-operative NV**
  - **Their effects is augmented by combination with corticosteroids and NK_1 antagonists.**

Side effects

- **Are minimal as they are well tolerated.**
- **Headache, dizziness and constipation.**
- **Minor ECG abnormalities (QT prolongation)**

D_2 receptor antagonists

- **block D_2 dopamine receptors in the CTZ**
- **Two types exist:**
  - Prokinetics drugs
  - Neuroleptics (antipsychotics)

D2 receptor antagonists

Prokinetics drugs

- **Domperidone: oral**
- **Metoclopramide: oral, i.v**
- **Are prokinetic agents (increased upper GI motility & gastric emptying).**

Uses

- **Prokinetic (5 HT4 agonist activity)**
  - **Gastroesophageal reflux disease (GERD)**
  - **Gastroparesis (impaired gastric emptying after surgery).**

- **Antiemetics (blocking D2 receptors in CTZ)**
  - **Effective against vomiting due to cytotoxic drugs, gastroenteritis, surgery, toxins, uremia, radiation**

Side effects (only for metoclopramide):

- ✓ **Dyskinesia (*extra-pyramidal side effects)*,**
- ✓ **Galactorrhea, menstrual disorders, impotence**
- ✓ **Postural hypotension (α-blocking action).**
- ✓ **Sedation, drowsiness**

Can domperidone produce these side effects?

Metoclopramide crosses BBB but domperidone Can not cross in a significant amount.

(both have antiemetic effects as CTZ has incomplete blood brain barrier).

Other D2 receptor antagonists

Neuroleptics (Antipsychotics)

- Chlorpromazine (CPZ), droperidol
- used for postoperative vomiting and chemotherapy-induced emesis.

Side effects:

- Extra pyramidal symptoms
- Sedation
- Postural hypotension

Neurokinin1 (NK1) receptor antagonists

Aprepitant

- **Acts centrally as substance P antagonist by blocking neurokinin 1 receptors in vagal afferent fibers in STN and area postrema.**
- **Orally**
- **Usually combined with 5-HT_3 antagonists and corticosteroids in prevention of chemotherapy-induced nausea and vomiting and post- operative NV.**

H_1-receptor antagonists

- **Include drugs as**
  - Diphenhydramine, Promethazine
  - Meclizine, Cyclizine

- **Used for**
  - Motion sickness
  - Morning sickness in pregnancy
  - Promethazine: severe morning sickness of pregnancy (if only essential).

Side effects:

- Prominent sedation
- Hypotension
- Anticholinergic effects or atropine like actions (dry mouth, dilated pupils, urinary retention, constipation).

Muscarinic receptor antagonists

- **Hyoscine (scopolamine)**
- **Orally, injection, patches**
- **Used as transdermal patches in motion sickness (applied to the postauricular area).**
- **Reduce impulses from vestibular apparatus**
- **Used for**
  - **Motion sickness**
  - **Not in chemotherapy-induced vomiting**

Side effects:

- **Sedation**
- **Tachycardia, blurred vision, dry mouth, constipation, urinary retention (atropine-like actions).**

Glucocorticoids

- **Dexamethasone - methylprednisolone**
- **Used in chemotherapy-induced vomiting**
- **combined with 5-HT_3 antagonists or NK1 receptor antagonists.**

Glucocorticoids

Side effects:

- Hyperglycemia
- Hypertension
- Cataract
- Osteoporosis
- Increased intraocular pressure
- Increased susceptibility to infection
- Increased appetite & obesity

Summary

The choice of antiemetic depends on the etiology

Motion sickness

Muscarinic antagonists

Antihistaminics

Vomiting with pregnancy (morning sickness)

Avoid all drugs in the first trimester

Pyridoxine (B6)

Promethazine (late pregnancy).

Drug- induced vomiting (CTZ), uremia, gastritis

Dopamine antagonists

Post operative nausea & vomiting

Dopamine antagonists

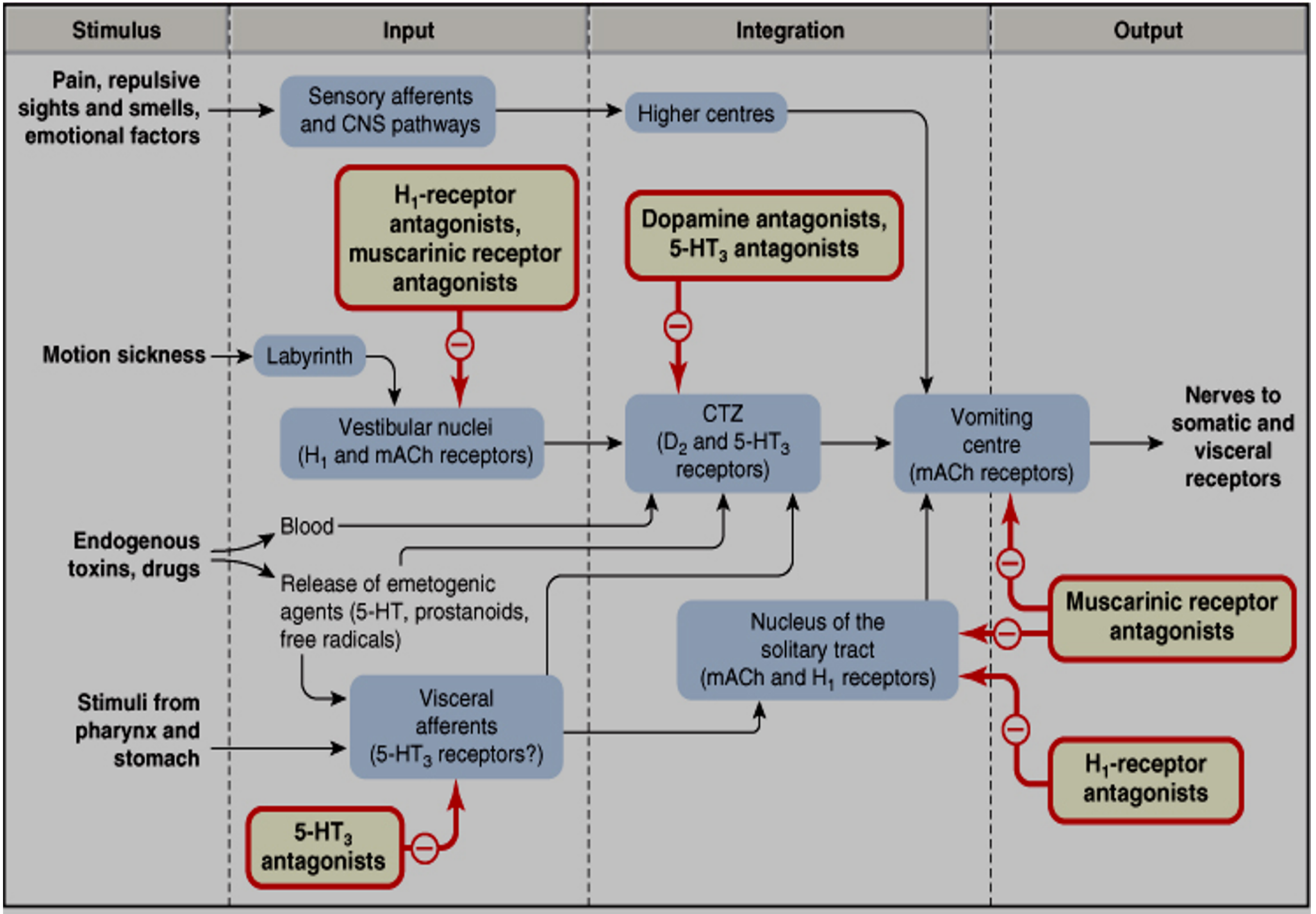
Vomiting due to cytotoxic drugs.

5-HT_3 antagonists

NK_1 antagonists

D_2- antagonists

Glucocorticoids



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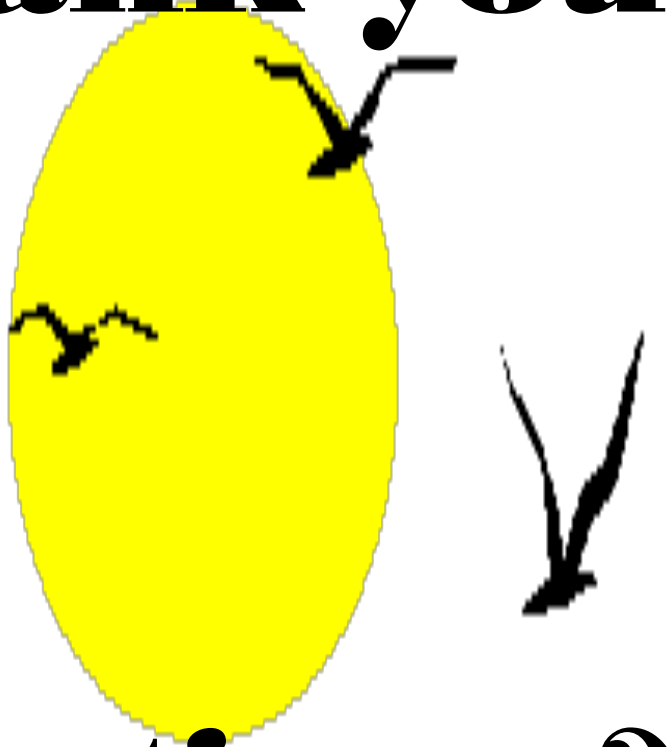

Questions ?