جامعة تكريت – كلية الطب البيطري

الدراسات العليا \ فرع الادوية والفسلجة والكيمياء الحياتية

ماجستير أدوية

أ د حسام الدين النجار

First Term \ 2024-2025

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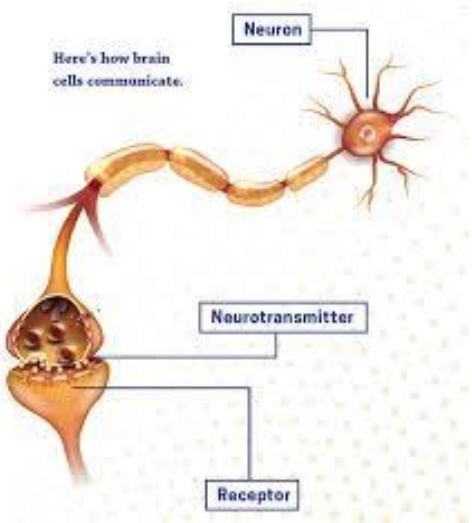
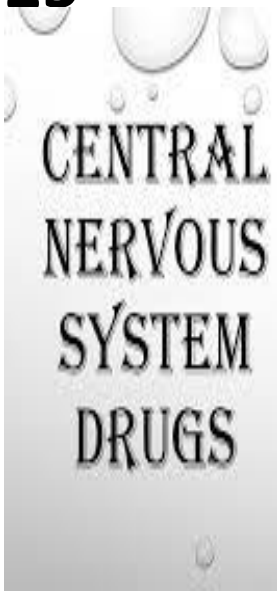
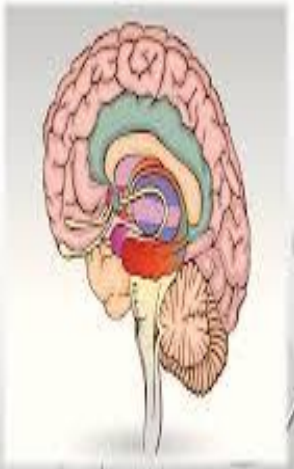


Advanced Pharmacology

CNS DRUGS





Drugs used in affective disorders: antidepressants

- Affective disorders are characterized by a disturbance of mood associated with alterations in behaviour, energy, appetite, sleep and weight.
- **The extremes range from intense excitement and elation (mania) to severe depressive states.**
- **In depression, which is much more common than mania, a person becomes persistently sad and unhappy.**
- **Depression is common and, although it can cause people to kill themselves, in general the prognosis is good.**

- **Most of the drugs used in the treatment of depression inhibit the reuptake of norepinephrine (NE) and/or serotonin (5HT) .**
- **The tricyclics are older drugs with proven efficacy, but are often sedative and have autonomic side-effects that may limit their use.**
- **The tricyclics are the most dangerous in overdosage, mainly because of cardiotoxicity, but convulsions are common.**
- **Selective serotonin reuptake inhibitors (SSRIs) are newer drugs that have a wide margin of safety and a different spectrum of side-effects (mainly gastrointestinal).**
- **Monoamine oxidase inhibitors (MAOIs) are used less often than other antidepressants because of dangerous interactions with some foods and drugs. A few antidepressants are receptor blockers and do not inhibit MAO or monoamine uptake.**

Pros and Cons of Antidepressants

Pros

Helps manage symptoms

Effective

Safe

Cons

Can cause side effects

Takes time to see results

Some may not work

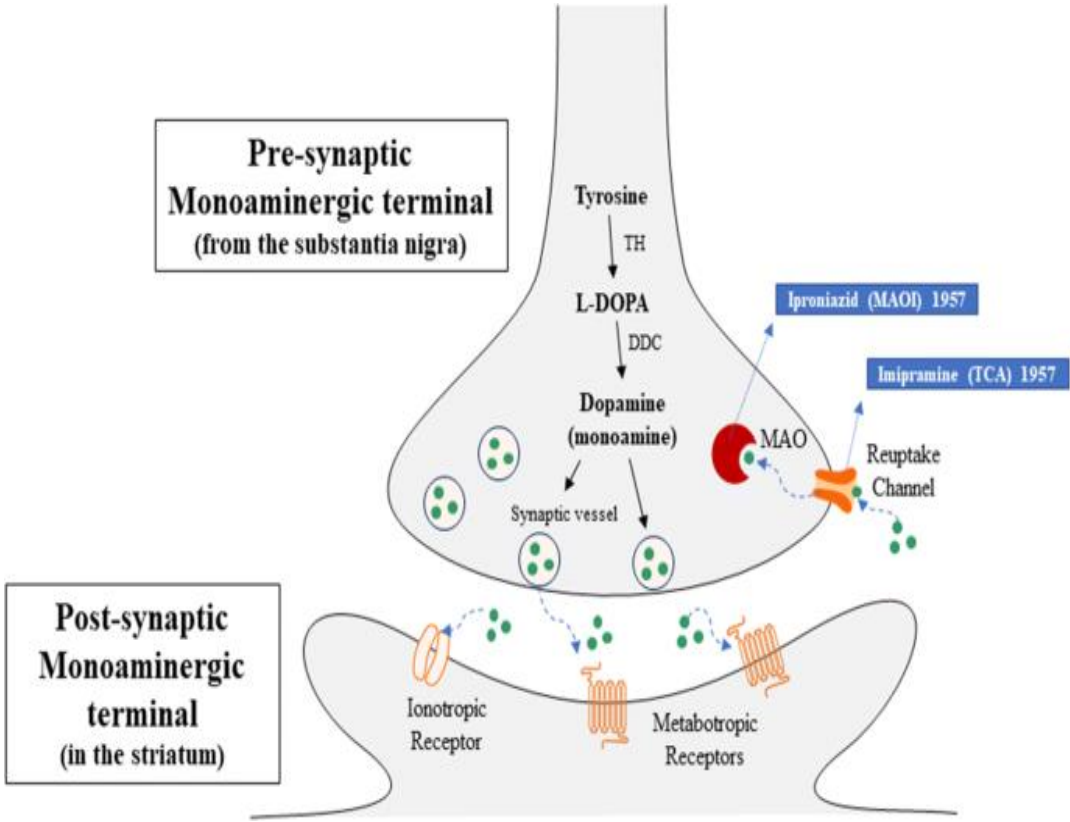
All antidepressants may provoke seizures and no particular drug is safe for the depressed epileptic patient.

A striking characteristic of antidepressant treatment with drugs is that the benefit does not become apparent for 2–3 weeks. The reason for this is unknown, but may be related to gradual changes in the sensitivity of central 5HT and/or adrenoceptors.

About 70% of patients respond satisfactorily to treatment with antidepressant drugs.

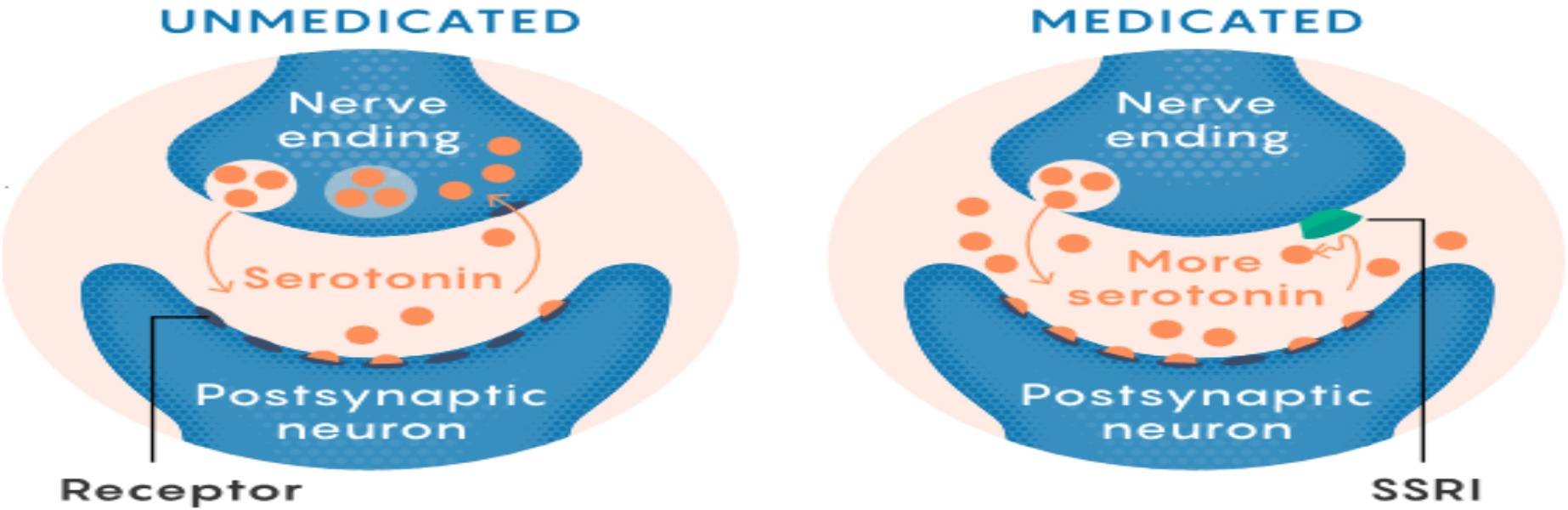
The cause of depression and the mechanism of action of antidepressants are unknown totally.

The monoamine theory was based on the idea that depression resulted from a decrease in the activity of central noradrenergic and/or serotonergic systems.



Boosting Serotonin

Drugs called selective serotonin reuptake inhibitors (SSRIs) raise serotonin levels in the brain. But their value as antidepressants may not stem from this effect.



After a neuron releases serotonin to stimulate a neighboring cell, it takes up the serotonin again.

By blocking reuptake, SSRIs raise the serotonin levels in the synapse.

- **In mania and in bipolar affective disorders (where mania alternates with depression), lithium has a mood-stabilizing action.**
- **Lithium salts have a low therapeutic/toxic ratio and adverse effects are common.**
- **Carbamazepine and valproate also have mood-stabilizing properties and can be used in cases of non-response or intolerance to lithium.**

- **Monoamine theory of depression:**

Reserpine, which depletes the brain of norepinephrine and serotonin, often causes depression. In contrast, the tricyclics and related compounds block the reuptake of norepinephrine and/or serotonin and the MAOIs increase their concentration in the brain.

Both of these actions increase the amounts of norepinephrine and/or serotonin available in the synaptic cleft.

There are several problems with the monoamine theory of depression. In particular, it has been difficult to understand why the tricyclic drugs rapidly block norepinephrine/serotonin uptake but require weeks of administration to achieve an antidepressant effect.

Mechanism of action of antidepressants

The mechanisms involved in antidepressant action are poorly under stood.

It is thought that SSRIs cause an increase in extracellular serotonin that initially activates autoreceptors, an action that inhibits serotonin release and reduces extracellular serotonin to its previous level.

However, with chronic treatment, the inhibitory autoreceptors desensitize and there is then a maintained increase in forebrain serotonin release that causes the therapeutic effects.

Drugs that inhibit norepinephrine uptake probably act indirectly, either by stimulating the serotonergic neurones (that have an excitatory noradrenergic input) or by desensitizing inhibitory presynaptic α2-receptors in the fore brain.

- **Drugs that inhibit amine uptake:**

The term 'tricyclic drug' refers to compounds based on the dibenzazepine (e.g. imipramine) and dibenzocycloheptadiene (e.g. amitriptyline) ring structures.

No individual tricyclic drug has superior antidepressant activity and the choice of drug is determined by the most acceptable or desired side-effects.

Thus, drugs with sedative actions, such as amitriptyline is more suitable for agitated and anxious patients and, if given at bedtime, will also act as a hypnotic.

- **The tricyclics resemble the phenothiazines in structure and have similar blocking actions at cholinergic muscarinic receptors, α-adrenoreceptors and histamine receptors.**
- **These actions frequently cause dry mouth, blurred vision, constipation, urinary retention, tachycardia and postural hypotension. In overdosage, the anticholinergic activity and quinidine-like action of the tricyclics on the heart may cause arrhythmias and sudden death.**
- **They are contraindicated after myocardial infarction. Amitriptyline particularly toxic in overdosage.**

- **The SSRIs do not have the troublesome autonomic side-effects or appetite-stimulating effects of the tricyclics, but do have different ones, the most common being nausea, vomiting, diarrhoea and constipation.**
- **They may also cause sexual dysfunction. The SSRIs are now generally accepted as first-line drugs, especially in patients with cardiovascular disease, those in whom any sedation must be avoided, or for those who cannot tolerate the anticholinergic effects of the tricyclics.**
- **SSRIs should not be given to patients under 18 years of age because they may increase the risk of suicidal behaviour. Venlafaxine inhibits the reuptake of both 5HT and (at higher doses) norepinephrine. It may have higher efficacy than other antidepressants. Its adverse effects generally resemble those of the SSRIs.**

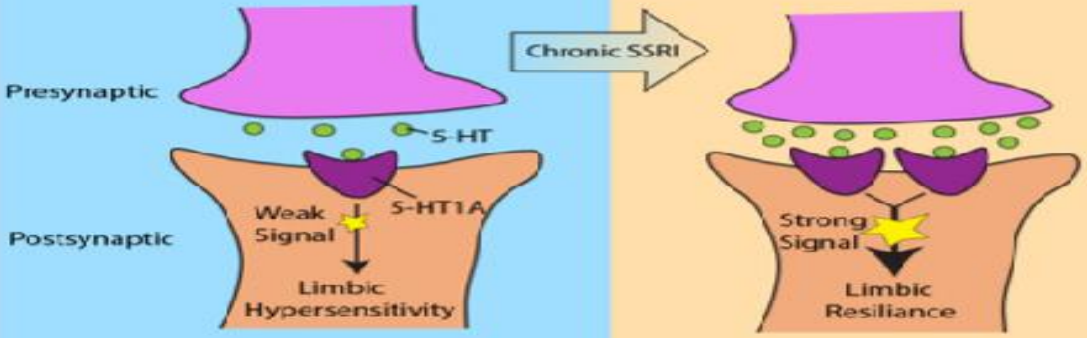
Bipartite Model of Serotonin in Depression

5-HTRs as a neuroprotective system: Post-synaptic 5-HT_{1A}

Depressed
- 5-HT_{1A} Signalling ↓
- Anxiogenesis ↑
- Impulsivity ↑
- Aggression ↑

Post-Treatment
- 5-HT_{1A} signalling ↑
- Patience ↑
- Resilience ↑
- Anxiety ↓

Limbic: 5-HT_{1A}-rich

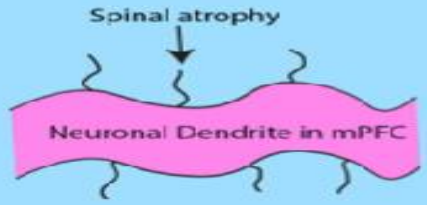


Outcome
- Stress Tolerance ↑
- Coping ↑
- HPA vicious cycle ↓

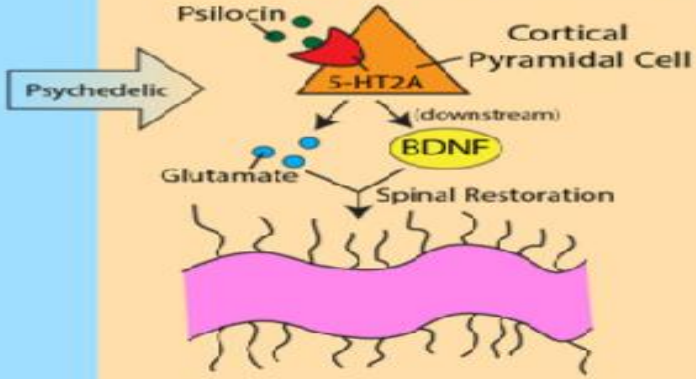
Depression ↓

5-HTRs as a therapeutic target: 5-HT_{2A}

Depressed
- Dysfuncitonal Emotional Circuits
- Dysfunctional Reward Circuits



Post-Treatment
- Neuroplasticity ↑
- Learning/Unlearning ↑
- Adaptability/Change ↑
- Environmental Sensitity ↑



Outcome
- Negative Emotional Bias ↓
- Positive Reward Appraisal ↑

Cortex: 5-HT_{2A}-rich

- **Receptor blockers:** These drugs have little or no activity on amine uptake. They generally cause fewer autonomic side-effects and, because they are less cardio toxic, they are less dangerous in overdosage.
- Mirtazapine and trazodone are sedative antidepressants.
- Mirtazapine has α2-adrenoceptor blocking activity and, by blocking inhibitory α2-autoreceptors on central noradrenergic nerve endings, it may increase the amount of norepinephrine in the synaptic cleft. Trazadone blocks 5HT2 receptors and increases 5HT release.

- **Monoamine oxidase inhibitors The older MAOIs (e.g. phenelzine) are irreversible non-selective inhibitors of monoamine oxidase.**
- **They are rarely used now because of their adverse effects (postural hypotension, dizziness, anticholinergic effects and liver damage) and interactions with sympathomimetic amines (e.g. ephedrine, often present in cough mixtures and decongestive preparations) or foods containing tyramine (e.g. cheese, game, alcoholic drinks), which may result in severe hypertension.**
- **Ingested tyramine is normally metabolized by monoamine oxidase in the gut wall and liver, but when the enzyme is inhibited, tyramine reaches the circulation and causes the release of norepinephrine from sympathetic nerve endings (indirect sympathomimetic action).**

LITHIUM

- **Lithium is used for prophylaxis in manic/depressive illness**.
- **It is also used in treatment of acute mania but, because it may take several days for the antimanic effect to develop, an antipsychotic drug is usually preferred for acutely disturbed patients.**
- **Lithium is used as an antidepressant in combination with tricyclics in refractory patients.**
- **Lithium is rapidly absorbed from the gut. The therapeutic and toxic doses are similar and serum lithium concentrations must be measured regularly (therapeutic range, 0.4–1.0 mM).**
- **Adverse effects include nausea, vomiting, anorexia, diarrhoea, tremor of the hands, polydipsia and polyuria (a few patients develop nephrogenic diabetes insipidus), hypothyroidism and weight gain.**
- Signs of lithium toxicity include drowsiness, ataxia and confusion, and, at serum levels above 2–3 mM, life-threatening seizures and coma may occur.

- Mechanism of action of lithium: **This is unknown, but probably involves interactions with second messenger systems.** In particular, lithium at concentrations of less than 1 mM blocks the phosphatidylinositol (PI) pathway at the point where inositol-1-phosphate is hydrolysed to inositol. **This causes depletion of membrane PIP2 and may reduce the actions of transmitters acting at receptors that involve inositol-1,4,5-trisphosphate/ diacylglycerol (InsP3/DG) as their second messengers.**

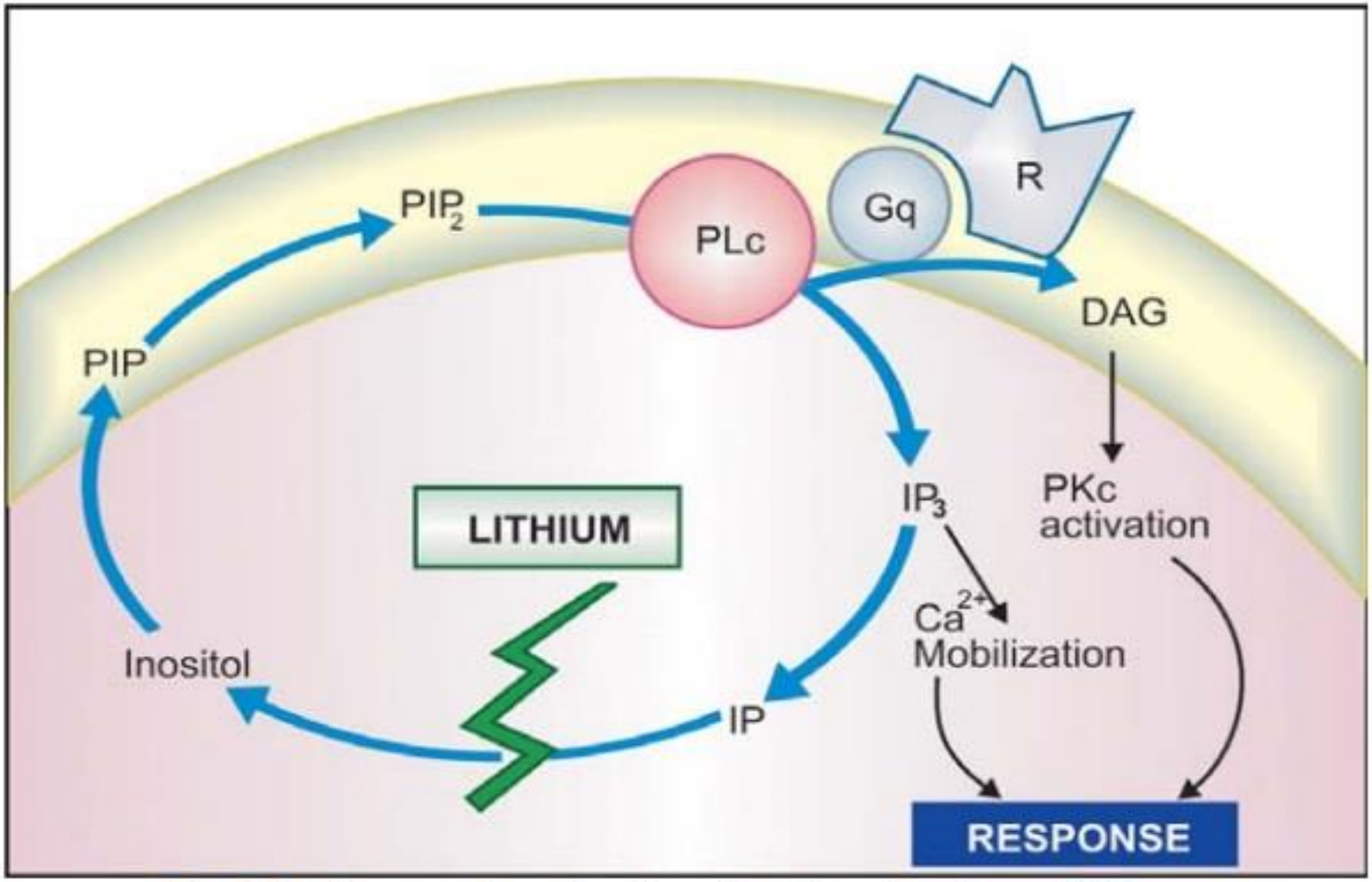
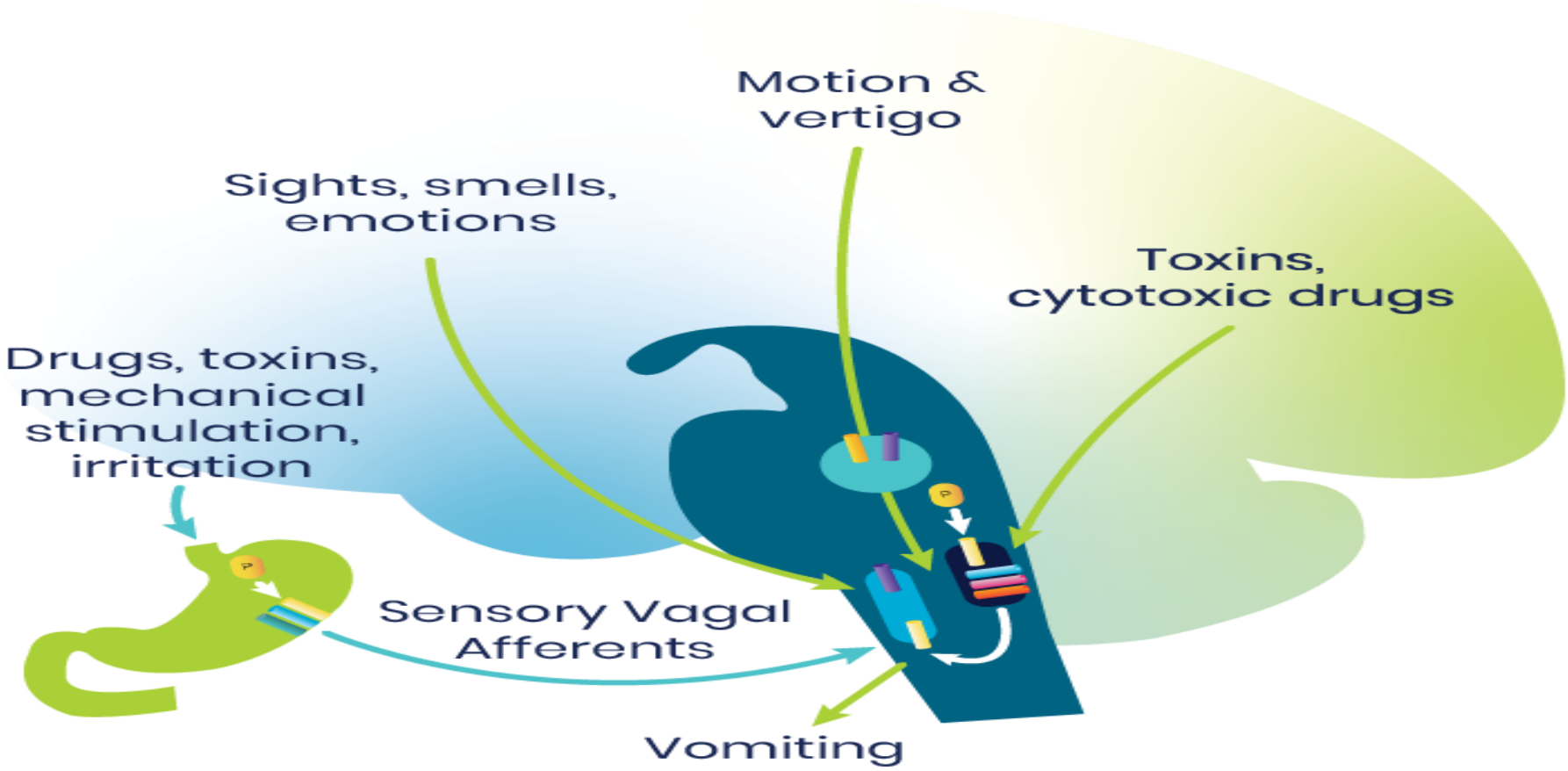


Fig. 32.1: Proposed mechanism of antimanic action of lithium
PIP—Phosphatidyl inositol phosphate; PIP_2—Phosphatidyl inositol bisphosphate; IP_3—Inositol trisphosphate; IP—Inositol-1-phosphate; PLc—Phospholipase C; DAG—Diacyl glycerol; PKc—Protein Kinase C; Gq—Coupling Gq protein; R—Neurotransmitter receptor

Drugs used in nausea and vertigo (antiemetics)

- **Nausea and vomiting have many causes, including drugs (e.g. cytotoxic agents, opioids, anaesthetics, digoxin), vestibular disease, provocative movement (e.g. Sea sickness), migraine and pregnancy.**
- **Vomiting is much easier to prevent than to stop once it has started. Therefore, if possible, antiemetics should be given well before the emetic stimulus is expected.**
- **Antiemetics should not be given before the diagnosis is known because identification of the underlying cause may be delayed.**

- **Emesis is coordinated by the vomiting centre in the medulla .**
- **An important source of stimulation of the vomiting centre is the chemoreceptor trigger zone (CTZ,) in the area postrema. Because the CTZ is not protected by the blood–brain barrier (it is part of the circumventricular system), it can be stimulated by circulating toxins or drugs .**
- **The CTZ possesses many dopamine (D2) receptors, which explains why dopaminergic drugs used in the treatment of Parkinson's disease frequently cause nausea and vomiting.**
- **However, dopamine receptor antagonists are antiemetics and are used to reduce nausea and vomiting associated with the administration of emetogenic drugs (e.g. many cytotoxic anticancer agents).**



Vestibular Nucleus

P Substance P

Vomiting Center

Chemoreceptor Trigger Zone

NK_1 Receptor

Muscarinic Receptor

ENK Receptor

H_1 Receptor

$5HT_3$ Receptor

$5HT_4$ Receptor

D_2 Receptor

- **The CTZ also possesses 5HT3 receptors, and 5HT3 antagonists (e.g. ondansetron) are effective antiemetics. Because they have fewer unwanted actions, they are widely used to prevent or reduce the nausea and vomiting associated with cancer chemotherapy and general anaesthesia.**
- **In some cases, it is uncertain how 5HT3 antagonists produce their antiemetic effects. There is a high concentration of 5HT3 receptors in the CTZ, but a peripheral action may also be important.**
- **Many cytotoxic drugs (and X- rays) cause the release of 5HT from enterochromaffin cells in the gut, and this activates 5HT3 receptors on vagal sensory fibres (Stimulation of sensory fibres in the stomach by irritants e.g. ipecacuanha, bacterial toxins) causes 'reflex' nausea and vomiting.**

- Dopamine antagonists and 5HT3 antagonists are ineffective in reducing the nausea and vomiting of motion sickness.
- Antimuscarinic drugs or antihistamines which act directly on the vomiting centre, may be effective, although side-effects are common.
- Vertigo and vomiting associated with vestibular disease are treated with anti histamines (e.g. promethazine, cinnarizine, phenothiazines or betahistine).
- Substance P given intravenously causes vomiting. Therefore, it was reasoned, antagonists of substance P might have an antiemetic action. This idea led to the introduction of aprepitant, a neurokinin-1 receptor antagonist.

- **The vomiting centre is in the lateral reticular formation of the medulla at the level of the olivary nuclei.**
- **It receives afferents from the following**: **1 Limbic cortex**. These afferents presumably account for the nausea associated with unpleasant odours and sights.
- **Cortical afferents are also involved in the conditioned vomiting reflex that may occur when patients see or smell the cytotoxic drugs they are about to receive.**
- **2 CTZ. 3 Nucleus solitarius.** These afferents complete the arc for the gag reflex (i.e. the reflex caused by poking a finger in the mouth). **4 Spinal cord** (spinoreticular fibres). These are involved in the nausea that accompanies physical injury. **5 Vestibular system**. These are involved in the nausea and vomiting associated with vestibular disease and motion sickness

- **The transmitters involved in the pathways concerned with emesis are not fully known.** However, the CTZ is rich in D2 dopamine and 5HT3 receptors.
- **Cholinergic and histaminergic synapses are involved in transmission from the vestibular apparatus to the vomiting centre.**
- **The vomiting centre projects to the vagus nerve and to the spinal motor neurones supplying the abdominal muscles. It is responsible for coordinating the complex events underlying emesis. Reverse peristalsis transfers the contents of the upper intestine into the stomach. The glottis closes, the breath is held, the oesophagus and gastric sphincter relax, and finally the abdominal muscles contract, ejecting the gastric contents**

- **Drug-induced vomiting** Cytotoxic drugs vary in their emetic potential, but some, e.g. cisplatin, cause severe vomiting in most patients.
- **The emetic action of these drugs seems to involve the CTZ, and the dopamine antagonists are often effective antiemetics.**
- **Prochlorperazine is a phenothiazine that has been widely used as an antiemetic. It is less sedative than chloropromazine, but may cause severe dystonic reactions (like all typical neuroleptics).**
- **Metoclopramide is a D2 antagonist, but also has a prokinetic action on the gut and increases the absorption of many drugs . This can be an advantage, e.g. in migraine, where the absorption of analgesics is enhanced. Adverse effects are usually mild, but severe dystonic reactions may occur (more commonly in the young and in females).**

- **Domperidone is similar to metoclopramide, but does not cross the blood–brain barrier and rarely causes sedation or extrapyramidal effects.**
- **The 5HT3 antagonists, e.g. ondansetron, lack the adverse effects of dopamine antagonists, but may cause constipation or headaches. It has been shown in clinical trials that the severe vomiting caused by highly emetic cytotoxic drugs is controlled better by combinations of intravenous antiemetic drugs,** e.g. metoclopramide and dexamethasone. A combination of ondansetron and dexamethasone will prevent cisplatin-induced emesis in most patients.
- **It is not known why dexamethasone is antiemetic.**

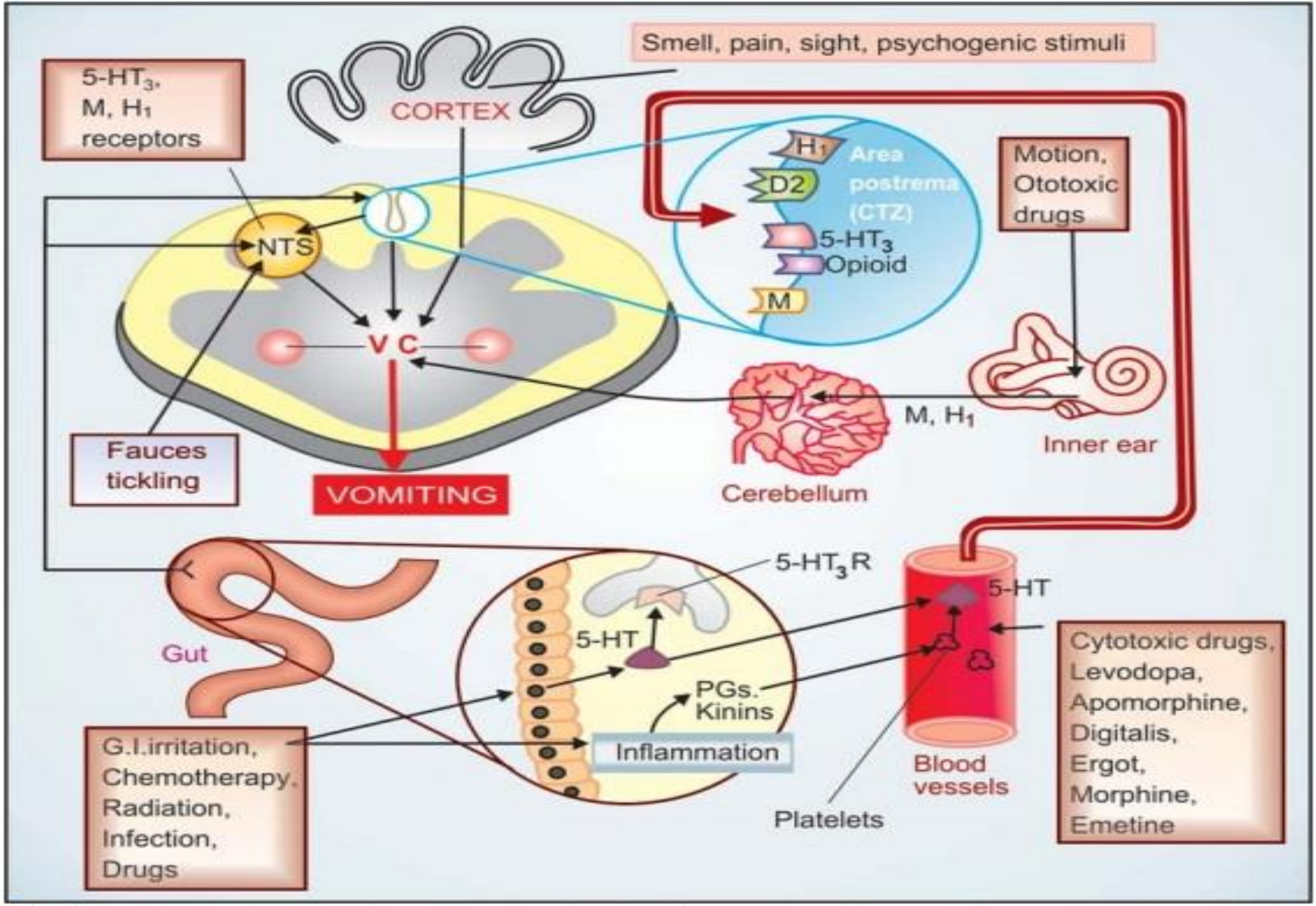


Fig. 47.1: Major central and visceral structures involved in emesis and the neurohumoral receptors mediating the emetic response. NTS: Nucleus tractus solitarius; VC: Vomiting centre; CTZ—Chemoreceptor trigger zone; 5-HT_3R: 5-HT_3 receptor