

Autacoids

INTRODUCTION

Autacoids are chemically diverse group of substances produced by various tissues in the body that cause slow contraction of smooth muscle; they have other intense but varied pharmacologic activities. The most important autacoids groups are:

I. **Biologically active amines** e.g. Histamine and Serotonin

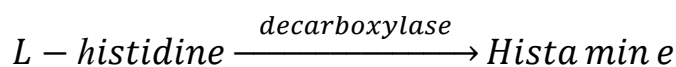
II. **Vasoactive polypeptides** e.g. Angiotensin and Kinins

III. **Eicosanoids** e.g. Prostaglandins and Leukotrienes

Histamine

Synthesis:

By decarboxylation of the amino acid L-histidine with L-aromatic amino acid decarboxylase enzyme



Storage:

In storage granules inside the mast cells (present in most tissues e.g. lung, skin and GIT)

Release:

- 1) **Histamine liberation:** histamine liberators are basic drugs (e.g. **morphine**, **atropine**, **curare**, **hydralazine**) that *replace histamine in the storage granule without degranulation*.
- 2) **Immunogenic release:** antigenic drugs (e.g. **penicillin**) induce the *release of the whole granules* from the sensitized mast cells through interaction with IgE on its surface. This action is mediated by increase intracellular calcium.

Pathogenic role of histamine:

- 1) **Allergy:** Histamine stimulates H₁-receptors leading to various types of immediate hypersensitivity reactions e.g.
 - a. **Local allergic response** localized H₁ receptors stimulation on the blood vessels and nerve endings (arterial dilatation induces redness; venous dilatation increases capillary permeability and induces edema; sensory nerve stimulation induces pain and itch)
 - b. **Anaphylactic shock:** generalized H₁ receptors stimulation induces marked arterial dilatation and hypotension.
 - c. **Bronchial asthma:** H₁ receptors stimulation on bronchial smooth muscles induces bronchospasm.
- 2) **Vomiting of vestibular origin** (e.g. motion sickness) is H₁-receptor mediated
- 3) **Peptic ulcer:** H₂ receptors mediates more than 70% of HCl secretion.

Relevant drugs:

- 1) **H₁ receptor blockers** (anti-histaminic drugs): for allergic reactions.
- 2) **H₂ receptor blockers** (e.g. famotidine): for acid-related disorders (see GIT module)
- 3) **Mast cell stabilizers** inhibit immunogenic histamine release (see chest module)

First Generation Antihistamines e.g. Chlorpheniramine Promethazine

Actions & Indications	Adverse effects
<ul style="list-style-type: none">• Anti-allergic effect; they oppose the allergic effects mediated by H₁ receptors → used in Allergic reactions e.g. rhinitis, urticaria, anaphylactic shock ¹	
Secondary to Autonomic receptor blockade	
1) M-receptors blockade: <ul style="list-style-type: none">• Antiemetic effect → used in Vomiting: e.g. motion sickness (Dimenhydrinate) & vomiting of pregnancy (Doxylamine)• Antiparkinsonian effect → used in Parkinsonism 2) α-receptors blockade:	Atropine-like adverse effects e.g. dry mouth Elderlies are susceptible to urine retention (<i>in males with prostatic enlargement</i>), constipation, confusion and disequilibrium. Postural hypotension
Secondary to CNS depression	
<ul style="list-style-type: none">• Sedation → used as OTC hypnotic• Antitussive effect → used in dry cough	Drowsiness is the most common adverse effect. Young children may have paradoxical agitation

New generations Antihistamines²

e.g. Azelastine³, Fexofenadine, Cetirizine, Loratadine, Desloratadine

These are more lipophobic with subsequent

- less transit across the blood brain barrier (with **less sedation**)
- delayed elimination (with **prolonged action** that permits single daily dosing)

However, they still have varying degrees of autonomic effects and at high doses they can cross the blood brain barrier leading to sedation.

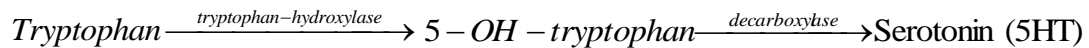
¹ In bronchial asthma; antihistaminics are not effective because they cannot antagonize the massive amounts of histamine released during the attack & because they cannot antagonize bronchospasm mediated by the *leukotrienes*. In anaphylactic shock, they are of help although not lifesaving.

² Terfenadine and Astemizole were withdrawn from the market since they led to prolongation of QT interval that progressed in some cases to ventricular tachycardia. esp with CYP3A4 enzyme inhibitors (e.g. erythromycin and with agents that additionally prolong QT-intervals (e.g. licorice).

³ It may be preferred by some patients with allergic rhinitis as it is available as a nasal spray

Serotonin (self-learning with migraine cases)

Synthesis:



Storage:

In GIT enterochromaffin cells, CNS neurones, and in platelets

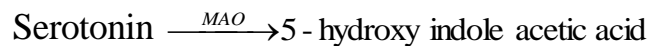
Release:

Release from blood platelets occurs following platelet activation e.g. by thrombin

Release from CNS neurons occurs on nervous stimulation

Metabolism:

By oxidation with monoamine oxidase into 5-hydroxyindole acetic acid; “5HIAA”



Reuptake:

Serotonin is re-uptaken by nerve endings in CNS by monoamine pump

Pathogenic role of serotonin:

- 1) **Anxiety:** 5HT_{1A} receptors stimulation in the limbic system reduces anxiety
- 2) **Migraine:** 5-HT_{1B/1D} receptors stimulation on cranial blood vessels and trigeminal nerve endings terminates acute migraine attack
- 3) **GIT motility disorders:** drugs which stimulate 5-HT₄ receptors or block 5HT₃ receptors have a “prokinetic action”
- 4) **Carcinoid syndrome:** serotonin stimulates smooth muscles contraction leading to bronchospasm and diarrhea
- 5) **Psychosis:** the role is not yet clear; however, the atypical antipsychotic drugs are serotonin receptor blockers
- 6) **Depression:** the role is not yet clear; however, most antidepressants increase central serotonin levels e.g. TCA, SSRI, NSRI, MAOIs. Some of these drugs also block 5HT₂ receptors.
- 7) **Vomiting:** some types of vomiting e.g. cancer chemotherapy-induced emesis is mediated by 5-HT₃ receptors stimulation
- 8) **Obesity:** 5HT_{2C} and possibly 5HT_{1B} receptors suppress appetite; this may be a target for some anorectic drugs

Relevant drugs:

1) Drugs which inhibit serotonin reuptake:

Selective serotonin reuptake inhibitors “SSRIs” e.g. Fluoxetine or non selective inhibitors e.g. *Norepinephrine-Serotonin reuptake inhibitors “NSRIs”* and

Tricyclic Anti-depressants “TCA” are used mainly in treatment of depression besides other indications; see CNS pharmacology.

2) Serotonin receptor agonists:

1. **Selective 5-HT_{1A} agonists** (e.g. **Buspirone**) are used as **selective anxiolytics**; see CNS pharmacology
2. **Selective 5-HT_{1B/1D} agonists** (**Triptans** and **Ergots**) are used as **anti-migraine** drugs
3. **Selective 5-HT₄ agonists** (**Prucalopride**, tegaderode, mosapride) used as prokinetics.

3) Serotonin receptors blockers:

1. **Selective 5HT₂ receptor blockers**
 - **Cyproheptadine and Pizotifen** block serotonin 5HT₂ as well as histamine H₁ receptors. Indications include:
 1. Conditions associated with excess serotonin (e.g. Postgastrectomy dumping syndrome, carcinoid syndrome and serotonin syndrome).
 2. OTC appetizers (common but non approved indication).
 - **Atypical antipsychotics** (e.g. risperidone) block 5HT₂ receptors in addition to blocking D₂ receptors; see CNS pharmacology
 - **Some antidepressants** (e.g. trazodone) block 5HT₂ receptors in addition to acting as SSRIs; see CNS pharmacology
2. **Selective 5HT₃ receptor blockers** (e.g. **Ondanosetron**; used as antiemetic and **alosetron**; used for diarrhea).

Toxicity of serotonin:

1) Valvular heart disease (chronic serotonin toxicity; anorectic drug toxicity⁴)

Serotonin stimulates fibrogenesis → thickening of the valve leaflets and chordae tendinae. The aortic and/or the mitral valves are usually affected while the tricuspid valve is involved in 50% of cases only.

2) Serotonin syndrome (acute serotonin toxicity)

It is a potentially life-threatening condition associated with increased serotonergic activity at postsynaptic 5-HT_{1A} and 5-HT_{2A} receptors in the CNS.

Aetiology:

It usually results from simultaneous administration of two serotonergic agents, but it can also occur with single serotonergic drug (especially SSRIs) at toxic dose or at therapeutic dose in serotonin-sensitive patients.

⁴ Chronic toxicity is seen in patients with carcinoid syndrome as well as during long term treatment with some serotonergic drugs. It was first described with the obsolete anorectic drugs Fenfluramine (a sympathomimetic amine that promotes the release of serotonin and blocks its neuronal uptake) and Dexfenfluramine (the dextroisomer of fenfluramine that is relatively selective to serotonergic pathways) when used in combination with phenentermine (e.g. fen/phen). It is suggested that 5HT_{2B} receptors stimulation plays an important role in this disease since drugs with low affinity for these receptors (e.g. trazodone, fluoxetine, and buspirone) are not associated valvular disease while drugs which are structurally similar to serotonin e.g. ergotamine, methysergide and pergolide were found to induce valve disease.

Clinical features:

The syndrome presents within 6-24 hours with non specific features:

- Changes in the mental status ⁵
- Autonomic manifestations ⁶
- Neuromuscular hyperactivity ⁷

Management:

1. **Discontinuation of all serotonergic agents:** the syndrome resolves within 24 hours of discontinuation but may persist longer with SSRI with long half life or MAOIs.
2. **Supportive care to normalize vital signs:**
 - **Severe hypertension and tachycardia** should be treated with short-acting agents, such as **nitroprusside and esmolol**.
 - **Hypotension from MAOIs** should be treated with low doses of direct-acting sympathomimetic amines such as **phenylephrine**.
 - **Hyperthermia > 41 °C** require **immediate sedation, paralysis** (*but not with succinylcholine*), and **endotracheal intubation** ⁸
 - **Agitation and convulsions** require sedation with **benzodiazepines**
3. **Administration of serotonin antagonists:**
 - **Cyproheptadine** is the recommended antidote.
 - **Atypical antipsychotic agents** with 5-HT_{2A} antagonist activity e.g. olanzapine or chlorpromazine may also be considered

⁵ These include anxiety, agitated delirium, restlessness, disorientation. Patients may startle easily.

⁶ These include tachycardia, hypertension, vomiting, and diarrhea, increased bowel sounds, dilated pupils, dry mucus membranes, flushed skin. Severe cases may develop diaphoresis, hyperthermia and dramatic swings in pulse and blood pressure.

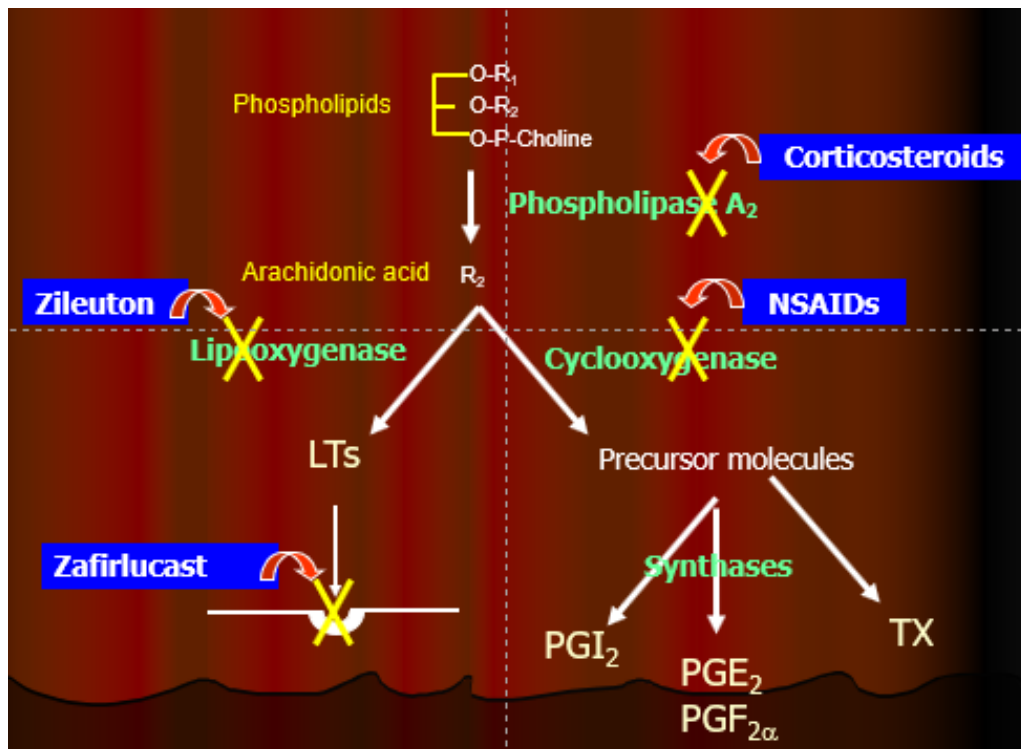
⁷ This manifests as tremor, muscle rigidity, myoclonus, ocular clonus (continuous, horizontal, eye movements), hyperreflexia, and bilateral Babinski sign

⁸ There is no role for antipyretic agents since the increase in body temperature is not due to an alteration in the hypothalamic temperature set point. Succinyl choline is not used as it induces initial increase in muscle activity (fasciculations).

Eicosanoids

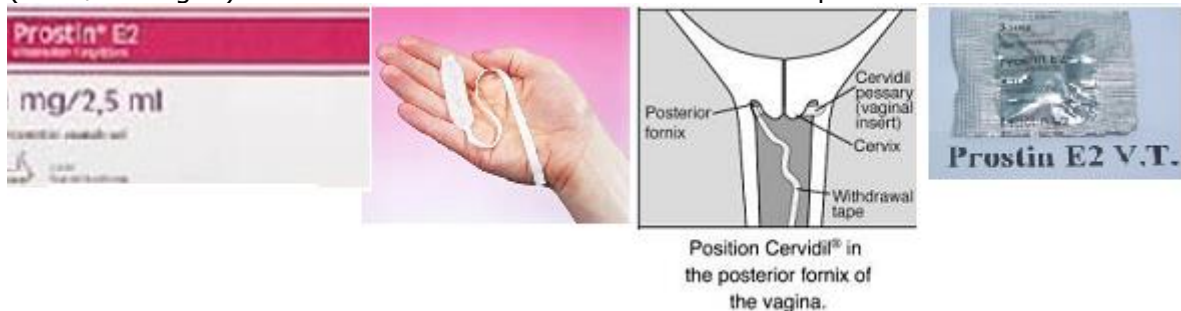
(Prostaglandins, Leukotrienes and Thromboxanes)

Synthesis and drugs acting on it:

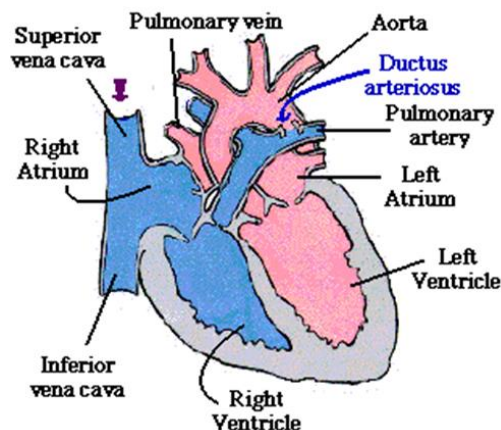


Pharmacological actions & Indications of PGs :

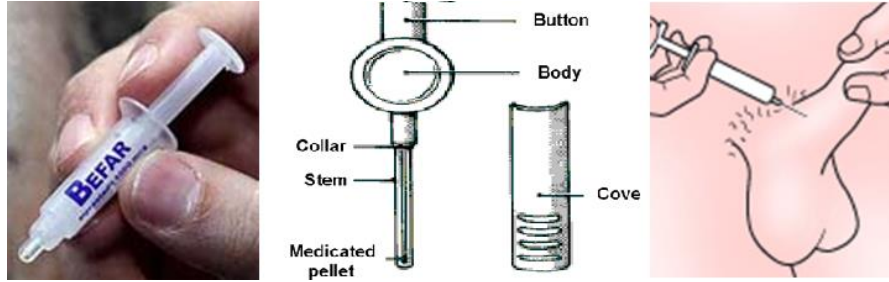
1. Uterus: **Contraction (ecbolic)** : by **PGE & PGF_{2α}** :
Local application of **Dinoprostone** (PGE₂ analogue) or **Dinoprost** (PGF_{2α}) and **Carboprost** (PGF_{2α} analogue) are used for Induction of labour and Therapeutic abortion.



2. Blood Vessels: **Vasodilatation** by **PGE₁**:
Alprostadil (PGE₁ analogue) is used To delay closure of PDA

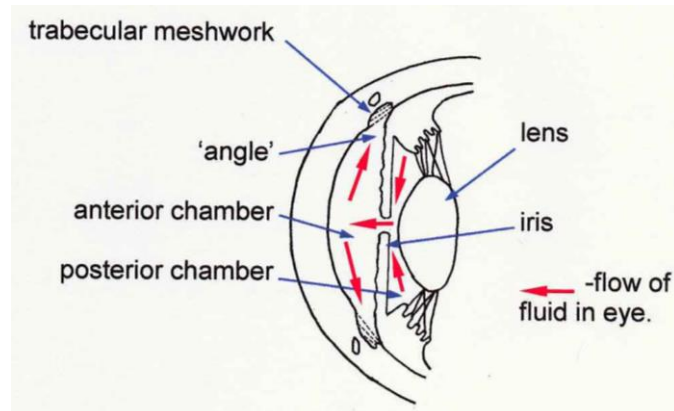


In erectile dysfunction.



3. Eye : **Aqueous drainage** by **PGF_{2α}**

Latanoprost (PGF_{2α} analog) is used in glaucoma.



4. GIT: **stimulate intestinal secretion & contraction & decrease HCl secretion:**

Lubiprostone (PGE₁ analogue): is used for idiopathic constipation.

Misoprostol (PGE₁ analogue) is used in NSAIDs-induced peptic ulcer.

5. Platelets: **PGI₂ (prostacyclin)** inhibits platelet aggregation + vasodilatation

PGI₂ analogues **Iloprost** (Inhalation) & **Beraprost** (Oral) for pulmonary hypertension.



Adverse effects of PGs:

1. Colic & diarrhea are the worst adverse effects.
2. May increase menstrual bleeding.
3. PGE₁ may induce local itching.
4. PGF_{2α} precipitates asthmatic attacks in asthmatics.
5. PGE₁ may → headache, dizziness & tachycardia