# CHAPTER 5

# AUTACOIDS AND THEIR ANTAGONISTS

**[1]Dr. Mukesh Kumar Kumawat**

[1]Assistant Professor, School of Pharmaceutical Sciences, Apeejay Stya University, Gurugram

**Ch.Id:-ASU/NSP/EB/HOP/2022/Ch-05**

**DOI:** https://doi.org/10.52458/9789391842529.nsp2022.eb.asu.ch5

## INTRODUCTION

"Autacoids (Greek for "self-healing") are a group of endogenous peptides, prostaglandins, leukotrienes, and cytokines. Local hormones are another name for them. They have many pharmacological implications as well as crucial roles in physiologic processes. Acute inflammation and wound healing are two intertwined responses that evolved to clear infections and noxious substances from the body and eventually restore tissue function and balance. Acute wound healing and inflammation are highly complicated reactions with overlapping time courses, shared cell types, and chemical mediators. Determining the roles of inflammation and leukocytes in wound healing has been a serious difficulty.

The risky activation of potent inflammatory responses that can entail friendly fire (e.g., leukocyte-mediated tissue injury), a critical problem in inflammatory illnesses and persistent wounds, has made pharmacological inhibition of the inflammatory response a major clinical goal. Indeed, elegant experiments using knockout and knockdown techniques show that increased inflammation slows wound healing. Therefore, Autacoids are chemicals that cells produce in response to various types of stimulation in order to trigger typical physiological responses locally. Pathological diseases like as inflammation, allergies, hypersensitivity, and ischaemia-reperfusion are all exacerbated by an imbalance in their synthesis, release, or transduction system.

**The following are some of the most important autacoids:**

1. **Biological Amines:** Histamine, Hydroxytryptamine (5-HT, Serotonin)
2. **Lipid-derived autacoids:**
   i. **Eicosanoids:** Prostaglandins, Leukotrienes, and Thromboxanes
   ii. **Platelet Activating Factors** (PAF)
3. **Polypeptides:** Kinins

**Histamine**

It's a strong tissue amine found in plant and animal tissues, as well as in bee venom. Decarboxylation of histidine produces it in humans, and the majority of it is stored in mast cells and basophils.

**Mechanisms of Action:** It works on two major receptor types.

a. Smooth muscle contraction, enhanced vascular permeability, and mucus formation are all caused by stimulation of H1 receptors. H1 antagonists compete with each other to inhibit these effects.
b. H2 receptor activation increases stomach acid production, which is prevented by H2 blockers like cimetidine.

Both types of receptors are involved in the production of edoema and vascular dilation.

**Pharmacological Actions:**

1. **Cardiovascular system:** Histamine causes capillary and venule dilation, as well as a drop in blood pressure. Direct relaxation of blood vessel smooth muscles is the process. Antihistaminic drugs are ineffective in reversing this effect, although adrenaline can.

   It also exerts inotropic and chronotropic effects on the heart, as well as impairing AV conduction and increasing coronary blood flow.
2. **Smooth Muscles:** The smooth muscles of several tissues, including the bronchi and uterus, are directly stimulated by histamine. Adrenaline efficiently counteracts histamine-induced bronchospasm.
3. **Exocrine Glands:** It is a potent stimulator of stomach mucosal HCl secretion.
4. **CNS:** Histamine is a "waking amine" that acts by "raising the sensitivity of broad cerebral areas to excitation signals" and is produced locally in the brain.
5. **Miscellaneous actions include itching and discomfort inducement:** Histamine presently has no proven therapeutic value. However, it is extremely critical in anaphylaxis and other allergic reactions. Its release can be triggered by venoms, medicines, trauma (thermal, chemical, or radiation), and antigen-antibody responses, among other things.

**Treatment of Anaphylaxis**

1. The problematic agent's exposure should be stopped.
2. Adrenaline operates as a physiological antagonist since its activities are the polar opposite of those of histamine. It can be delivered via SC or IM.
3. Intravenous fluid infusions should be used to treat hypotension.
4. Corticosteroids are employed on occasion.
5. Other supporting interventions include oxygen supply and, if necessary, artificial respiration.

Antihistaminic drugs are ineffective in treating anaphylactic shock, which causes hypotension and brochospasm.

**Antihistaminc Drugs**

**These drugs competitively block histamine receptors and are of two types:**

1. $H_1$ receptor antagonists
2. $H_2$ receptor antagonists (used in the treatment of acid-peptic disease)

**$H_1$ Receptor Antagonists**

**Classification of H1 receprior antagonists**:

1. Sedative and potent: diphenhydramine and promethazine, for example.
2. Sedative but not as potent as cyclizine and chlorpheniramine
2. Pheniramine, for example, is less powerful and sedative.
3. Terfenadine, loratadine, and cetrizine are examples of non-sedatives.

The latest generation of drugs has fewer central depressive effects. These substances may also have anti-emetic properties.

**Pharmacological Actions:**

1. **Antihistaminic Actions:** They inhibit the effects of histamine at diverse places.
2. **Other Effects:** These are unrelated to antihistaminic effects and vary greatly depending on the drug.

The majority of them cause CNS depression, which causes sleepiness, drowsiness, difficulty to concentrate, and coordination problems. However, only a few substances, such as phenindamine, can cause stimulation. Promethazine, diphenhydramine, and dimenhydinate all have anti-motion sickness properties. Promethazine and mepyramine are both effective local anaesthetics. The majority have atropine-like properties. Some have antimuscarinic properties in the central nervous system, which can help with Parkinson's disease treatment.

**Pharmacokinetics:** After oral and parenteral administration, they are well absorbed. And are metabolised mostly by the liver; breakdown products are excreted in the urine.

**Therapeutic Uses:**

1. **Allergic Disorders:** Urticaria, seasonal hay fever, atopic and contact dermatitis, and minor blood transfusion responses are all examples of allergic disorders. **N.**

**B.** Because of the risk of sensitization and a high potential to trigger eczematous reactions, they are not advised for topical use. They are not effective in bronchial asthma and common cold.

2. **Other uses:** Hypnotics include diphehydramine and promethazine. Parkinsonism can be effectively treated with diphenhydramine and orphenadrine. Motion sickness, other vomiting problems related with labyrinthine dysfunction, as well as nausea and vomiting linked with pregnancy, are all treated with dimehydrinate and promethazine. Diphenhydramine is widely used in combination preparations with other medicines to treat cough.

**Adverse Effects:**

They are often mild. Sedation is the most typical method. The most prevalent anticholinergic side effect is mouth dryness. They may trigger allergic reactions in certain people.

**5-Hydroxytreptamine (5-HT, Serotonin)**

It can be found in both plants and mammals. In animals, the pineal gland has the highest concentration, which acts as a precursor to melatonin. It's made up of the amino acid tryptophan and works on a variety of receptors.

Pharmacolocial Actions:

Renal, splanchnic, meningeal, and pulmonary arteries and veins and venules are constricted by 5-HT, but skeletal musle blood vessels, coronaries, and skin capillaries are dilated. On the myocardium, it exhibits a mild direct ino-chronotropic action. Smooth muscles, particularly those of the intestines, are also stimulated. Serotonin is a neurotransmitter that is broadly distributed throughout the CNS. Sleep, mood, sexual behaviour, motor activity, pain perception, migraine, temperature regulation, endocrine control, mental problems, and extrapyramidal activity may all be caused by altered functioning.

**Serotonin Agonists**

Sumatriptan is a 5-HT1 receptor selective agonist that is particularly effective in treating acute migraine attacks but not in preventing them. It improves nausea and vomiting, but the headache may return, requiring more treatments. It can be taken orally or applied subcutaneously. The oral dose has a bioavailability of just 14%, making it several times greater than the subcutaneous dose. Flushing and heat at the injection site, neck pain, disorientation, and tingling in the hands are all possible side effects. Because it may produce coronary vasoconstriction, the drug is not recommended for

people with symptomatic ischemic heart disease, angina, or hypertension. Another serotonin agonist, buspirone, is an excellent anxiolytic drug.

**Serotonin Antagonists:**

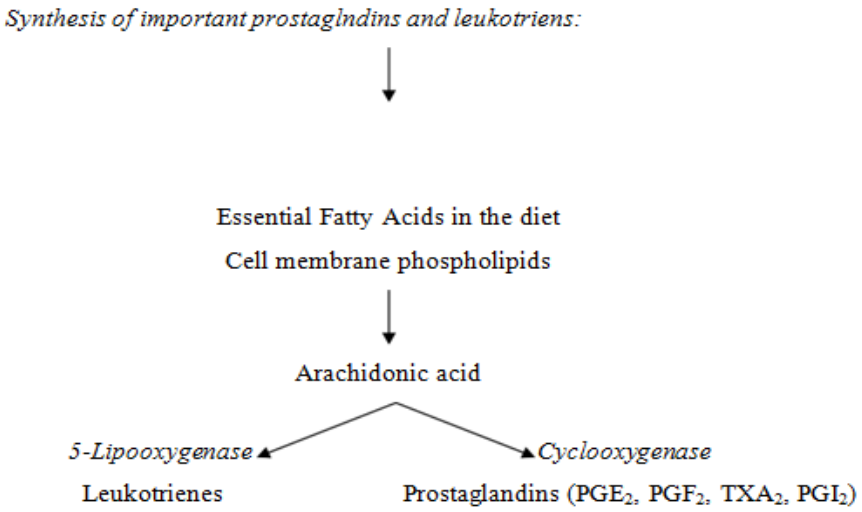
a. **Methysergide:** Prevents 5-HT from acting on a number of smooth muscles. It has a minor direct vasoconstrictor action as well. Migraine headaches can be prevented using this medication. However, it has no effect on acute episodes and may potentially make them worse. GI irritation, sleepiness, vertigo, and psychic problems are some of the side effects.
b. **Cyproheptadine** is a strong antagonist of 5-HT, as well as histamine and acetylcholine to a lesser extent. It promotes appetite by acting on the hypothalamus directly. It inhibits the production of aldosterone and the release of hydrocortisone. It's mostly used to treat itching caused by skin conditions including allergic dermatitis. Drowsiness is the most common side effect.
c. **Ondansetron** is a 5-HT3 receptor antagonist that is selective. It helps to alleviate nausea and vomiting caused by cytotoxic therapy when taken orally or intravenously. Headache, constipation, and allergic responses are some of the side effects.
d. **Anti-5-HT agents** such as prochlorperazine and haloperidol are sometimes used to treat resistant acute episodes.

**Prostaglandins**

They were given this name because of their purported prostate gland origin. The richest known source is human seminal fluid, however they can also be found in numerous tissues. At their action sites, prostaglandins are made from polyunsaturated fatty acids. The two primary prostaglandins are PG E2 and PG F2. Mechanical, chemical, and viral assaults release them into the body.

In conjunction with other mediators, they play a significant role in the development of the inflammatory response.

*ISBN- 978-93-91842-52-9* 




**Pharmacological Actions:**

**a.** Smooth muscle stimulates the myometrium and is believed to help with the initiation and maintenance of labour. Prostaglandin E acts as a bronchodilator.

**b.** **Gastrointestinal tract:** they improve intestinal motility. PG-E decreases stomach acid output and protects the gastroduodenal mucosa from damage. Both PG-E and F cause the gut's longitudinal muscle to contract. They also cause diarrhoea by stimulating intestinal fluid secretion.

**c.** **CVS:** PG-E is a potent natriuretic and peripheral vasodilator. PG-F causes arterioles and veins to contract.

**d.** Thromobxane promotes platelet aggregation and vasoconstriction in platelets. PG-I (prostacycline) is a strong inhibitor of platelet aggregation and a vasodilator found in the vascular endothelium.

**e.** **Other:** Prostaglandins play a role in pain creation and perception. PG-E and PG-I cause hyperalgesia, which is linked to inflammation. Furthermore, PG-E is a pyrogenic chemical.

Because of their brief duration of action, natural prostaglandins have little therapeutic use, but their derivatives such as carboprost, dinoprostone, and misoprostol do. Cervical ripening and labour induction, postpartum haemorrhage control, abortion induction, and NSAID-induced peptic ulcer prevention are just few of the therapeutic uses. Erectile dysfunction, glaucoma, and other conditions are among the more recent applications.

Fever, diarrhoea, abdominal cramps, headache, nausea, and vomiting are some of the potential side effects. Cervical ripening and labour induction, postpartum haemorrhage control, abortion induction, and NSAID-induced peptic ulcer prevention are just few of the therapeutic uses. Erectile dysfunction, glaucoma, and other conditions are among the more recent applications.

Fever, diarrhoea, abdominal cramps, headache, nausea, and vomiting are some of the potential side effects.

**Questions**

i. Describe the antagonistic effects of histamine & adrenaline.

ii. Explain the consequences of inhibition of prostaglandin synthesis.

*ISBN- 978-93-91842-52-9* 