**PHARMACOLOGY III**

**AUTACOIDS**

**Learning Objectives:**

After going through this unit, the student will be able to:

1. Explain the role of histamine in anaphylactic reactions

2. List some of the therapeutic uses and adverse effects of H1 antagonists

3. Describe the major pharmacological actions of prostaglandins E and F

**INTRODUCTION**

“Autacoids” (Greek “self-remedy”) is a collective term for various endogenous peptides,

prostaglandins, leukotrienes, and cytokines. These are sometimes also called local hormones.

They play important roles in physiologic processes and also have several pharmacological

significances.

**1. Histamine**

It is a potent tissue amine widely distributed in plant and animal tissues and in the venoms of

bees. In man, it is formed by decarboxylation of histidine and major portion is stored in mast

cells and basophils.

**Mechanisms of Action**: It acts on 2 major types of receptors

a. Stimulation of H1 receptors results in smooth muscle contraction, increased vascular

permeability, and mucus production. These effects are blocked competitively by H1

antagonists.

b. Activation of H2 receptors increases gastric acid production, and this effect is blocked by H2

blockers such as cimetidine.

Both types of receptors are involved in vascular dilatation and edema formation.

**Pharmacological Actions:**

1. ***Cardiovascular system***

Histamine produces dilatation of capillaries and venules accompanied by a fall in blood

pressure. The mechanism is direct relaxation of the smooth muscles of blood vessels. This

effect cannot be adequately reversed by antihistaminic agents but by adrenaline.

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It also has positive inotropic and chronotropic actions on the heart, impairs AV conduction, and

increases coronary blood flow.

2. ***Smooth Muscles***:

Histamine directly stimulates the smooth muscles of various tissues including the bronchi and

uterus. Histamine-induced bronchospasm is effectively antagonized by adrenaline.

3. ***Exocrine Glands***:

It is a powerful stimulant of HCl secretion by the gastric mucosa.

4. ***CNS***: Histamine is formed locally in the brain and is believed to be a “waking amine”, acting

by “increasing the sensitivity of large cerebral areas to excitation inputs”

5. ***Miscellaneous*** actions include induction of itching and pain.

Histamine has no valid therapeutic use currently. But it plays very important role in anaphylaxis

and other forms of allergic reactions. Its release may be induced by various agents including

certain venoms, drugs, trauma (thermal, chemical, radiation), and antigen-antibody reactions.

**Treatment of Anaphylaxis**

1. Exposure to the offending agent should be terminated.

2. Adrenaline has actions opposite to those of histamine and thus acts as a physiological

antagonist. It may be given by SC or IM route.

3. Hypotension should be corrected with the infusion of intravenous fluids.

4. Corticosteroids are occasionally used.

5. Other supportive measures include administration of oxygen and artificial respiration if

necessary.

**N.B.** Antihistaminic drugs are not able to counteract the hypotension and brochospasm

characteristic of anaphylactic shock.

**Antihistaminc Drugs**

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

1. H1 receptor antagonists

2. H2 receptor antagonists (used in the treatment of acid-peptic disease)

**H1 Receptor Antagonists**

**Classification of H1 recepror antagonists**:

1. Potent and sedative: such as diphenhydramine and promethazine.

2. Potent but less sedative: such as cyclizine and chlorpheniramine

3. Less potent and less sedative: such as pheniramine

4. Non-sedative: such as terfenadine, loratadine, and cetrizine.

The newer generation agents are relatively free of central depressant effects.

These agents may also possess anti-emetic effects.

***Pharmacological Actions***:

1. Antihistaminic Actions:-they block histamine effects at various sites.

2. Other Effects: are independent of the antihistaminic effects and vary widely according to

the drug used.

Most of them produce CNS depression resulting in sedation, drowsiness, inability to

concentrate, and disturbances of coordination. But very few agents such as phenindamine may

produce stimulation.Anti-motion sickness effects are exhibited by promethazine,

diphenhydramine, and dimenhydinate.Promethazine and mepyramine have significant local

anesthetic effect.Majority possess atropine-like effects.Some have central antimuscarinic

actions which is useful in the treatment of Parkinsonism.

***Pharmacokinetics:***

They are well-absorbed following oral and parenteral administration. And are mainly

metabolized by the liver; degradation products are removed in the urine.

***Therapeutic Uses:***

**1. *Allergic Disorders***:-Including urticaria, seasonal hay fever, atopic and contact dermatitis,

mild blood transfusion reactions.

**N.B.** Their topical use is not recommended because of the risk of sensitization and a high

tendency to cause eczematous reactions.

They are not effective in bronchial asthma and common cold.

**2. *Other uses:***

Diphehydramine and promethazine are used as hypnotics. Diphenhydramine and orphenadrine

are effective in the treatment of Parkinsonism .Dimehydrinate and promethazine are employed

in the prevention and treatment of motion sickness, other vomiting disorders associated with

labyrinthine dysfunction as well as nausea and vomiting associated with pregnancy.

Diphenhydramine is frequently used in the treatment of cough as combination preparation with

other agents.

***Adverse Effects:***

- Are usually mild. Most common is sedation. The most common anticholinergic adverse effect

is dryness of the mouth. They may themselves occasionally cause allergic reactions.

**2. 5-Hydroxytreptamine (Serotonin)**

It is widely distributed in plants and animals. Highest concentration in mammals is found in the

pineal gland, acting as a precursor for melatonin. It is synthesized from the amino acid

tryptophan and acts on several types of receptors.

***Pharmacolocial Actions:***

5-HT causes constriction of renal, splanchnic, meningeal, and pulmonary arteries and veins and

venules, but dilatation of the blood vessels of skeletal musles, coronaries, and skin capillaries. It

has weak direct iono-chronotropic effect on the myocardium. It also stimulates smooth muscles,

especially of the intestines. Serotonin is widely distributed in the CNS, serving as a

neurotransmitter. Altered functions may be responsible for disturbances in sleep, mood, sexual

behavior, motor activity, pain perception, migraine, temperature regulation, endocrine control,

psychiatric disorders and extra-pyramidal activity.

***Serotonin Agonists***:

***Sumatriptan*** is a selective agonist of 5-HT1 receptors and is highly effective in treating acute

attacks of migraine, but is not useful in the prevention. It relieves the nausea and vomiting, but

the headache may recur, necessitating repeated administrations.

It is administered orally or by the subcutaneous route. The bioavailability of oral dose is only 14

%; thus, the oral dose is several times larger than the subcutaneous dose.

Adverse effects include flushing and heat at the injection site, neck pain, dizziness, and tingling

of the hands.

The drug is contraindicated with symptomatic ischemic heart diseases, angina, and

hypertension as it may cause coronary vasoconstriction.

***Buspirone***, another serotonin agonist, is a useful effective anxiolytic agent.

**Serotonin Antagonists:**

a. ***Methysergide:*** blocks the actions of 5-HT on a variety of smooth muscles. It also has a

weak direct vasoconstrictor effect. It is an effective prophylactic agent for migrainous

headaches. But has no effect in treating acute attacks, even may worsen the condition.

Adverse reactions include gastrointestinal irritation, drowsiness, vertigo, and psychic

disturbances.

b. ***Cyproheptadine:*** is a potent antagonist of 5-HT and to a smaller extent of histamine and

acetylcholine. It stimulates appetite probably by acting directly on the hypothalamus. It can

block the release of hydrocortisone, and the production of aldosterone. It is mainly used to

relieve the itching associated with skin disorders such as allergic dermatitis. The common

adverse reaction is drowsiness.

c. ***Ondansetron***: is specific 5-HT3 receptor antagonist. Given orally or intravenously, it is

useful in the management of nausea and vomiting associated with cytotoxic therapy.

Adverse reactions include headache, constipation, and allergic reactions.

d. Prochlorperazine and haloperidol have anti-5-HT activity and are sometimes used for

resistant acute attacks.

**3. Prostaglandins:**

They were named so because of their presumed origin from the prostate gland. Human seminal

fluid is the richest known source, but they are also present in various tissues. The

prostaglandins are synthesized from polyunsaturated fatty acids at their sites of action. PG E2

and PG F2 are the two main prostaglandins. They are released in the body by mechanical,

chemical, and infectious insults.

They play an important role in the development of the inflammatory response in association with

other mediators.

***Synthesis of important prostaglandins and leukotriens:***

Essential Fatty Acids in the diet

Cell membrane phospholipids

Arachidonic acid

***5-Lipooxygenase Cyclooxygenase***

Leukotrienes Prostaglandins (PGE2, PGF2, TXA2, PGI2)

***Pharmacological Actions:***

a. Smooth muscle: most stimulate myometrium and are known to be important in the initiation

and maintenance of labor. Prostaglandin E has bronchodilator action.

b. GIT: they increase intestinal motility. PG E inhibits gastric acid secretion and has

cytoprotective action on the gastroduodenal mucosa. Both PG E and F produce contraction

of the longitudinal muscle of the gut. They also stimulate intestinal fluid secretion, resulting

in diarrhea.

c. CVS: PGE is peripheral vasodilator and powerful natriuretic. PGF constricts arterioles and

veins.

d. Platelets: Thromobxane causes platelet aggregation and vasoconstriction. PG I

(prostacycline) is found in the vascular endothelium and is a potent inhibitor of platelet

aggregation and is a vasodilator.

e. Miscellaneous: Prostaglandins are important in pain generation and perception. PGE and

PGI produce hyperalgesia associated with inflammation. In addition, PG E is a potent

pyrogenic substance.

Natural prostaglandins have no therapeutic application because of short duration of action, but

their derivatives such as carboprost, dinoprostone and misoprostol find clinical application.

***Therapeutic uses include c***ervical ripening and labor induction, control of postpartum

hemorrhage, induction of abortion, and prophylaxis of NSAID-induced peptic ulcers. They are

also finding several other uses more recently such as erectile dysfunction, glaucoma, etc.

***Adverse Effects*** include fever, diarrhea, abdominal cramps, headache, nausea, and vomiting.

**Exercise**

1. Explain the antagonistic effects of histamine and adrenaline.

2. Discuss the consequences of inhibition of prostaglandin synthesis.