UNIT 7 AUTACOIDS

Structure

7.1 INTRODUCTION

In the previous unit, you have learnt about the drugs acting on urinary system e.g. diuretics which increase the urine formation and are used in the treatment of various inflammation of the body. In this unit you shall study about the various autacoids secreted from the human body.

Objectives

After studying this unit, you should be able to:

- discuss the pharmacology of autacoids;
- know about the different receptor antagonists;
- enumerate the therapeutic uses of anti-histaminics and 5-HT antagonists; and
- enumerate the clinical uses of prostaglandins.

7.2 WHAT IS AUTACOIDS?

In the previous unit, you have learnt about the drugs acting on urinary system e.g. diuretics which increase the urine formation and are used in the treatment of various inflammation of the body. In this unit you shall study about the various autacoids secreted from the human body.

The term 'autacoid' is derived from Greek, *autos* – self and *akos* – remedy. These are formed in various tissues of the body and generally act locally at the site of synthesis and release in the body. They have also been called **'local hormones'** and differ from hormones which are secreted from endocrine glands. The hormones are produced by specific cells (endocrine glands), and are transported through circulation to the distant target organs while autacoids are produced in tissues rather than in glands.

The important autacoids include:

- Histamine,
- Hydroxytryptamine (5-HT, serotonin),
- Prostaglandins,
- Leukotrienes, and
- Kinins.

7.3 HISTAMINE

7.3.1 Histamine

Histamine is a potent biogenic amine, occurs in tissues in almost all forms of life and released in a free state in response to injury or to any antigen-antibody reaction. Histamine is formed by decarboxylation of the amino acid L-histidine, a reaction catalyzed by the enzyme histidine decarboxylase.

Histamine is found in most of the tissues, present in various biological fluids. In most tissues, histamine exists in granules, in mast cells or basophils. These mast cells are especially rich at sites of potential tissue injury i.e. skin, lungs, liver, GIT etc. and are unevenly distributed. It is also present in many venoms (of bees & wasps), bacteria and plant tissues.

Histamine Receptors

The present evidence indicates that histamine mainly act on two types of receptors namely H_1 and H_2 which are used clinically.

The contraction of smooth muscle, increase in vascular permeability and mucus secretion are mediated by H_1 receptors. These types of effects are competitively blocked by H_1 receptor antagonists (antihistaminics) like mepyramine.

7.4 ANTIHISTAMINIC AGENTS

Most of the antihistaminics (H_1-receptor antagonists) have similar pharmacological actions and conventionally can be discussed together. The antihistaminics blocks histamine effects at a variety of sites. They inhibit most responses of smooth muscles to histamine. They antagonize the stimulant actions of histamine on various smooth muscles of the respiratory system, gastrointestinal tract, the uterus and the blood vessels.

7.4.1 First Generation Antihistaminics

Majority of antihistaminic drugs (first generation antihistaminics e.g. diphenhydramine, pheniramine, maleate, promethazine, cyclizine etc.) produce variable degree of CNS depression i.e. sedation, drowsiness and sleep. Drugs like diphenhydramine, promethazine are potent sedatives and are often accompanied by inability to concentrate. The newer H_1-antagonists such as loratidine and cetrizine are claimed to have little or no sedative action.

Antihistaminics have a widespread value in the symptomatic treatment of various disorders. Some of the important therapeutic uses of this class of drugs are as follows:

Uses

a) **Hypersensitivity reactions:** To prevent allergic reactions or to treat their symptoms, in which histamine is the primary mediator. They are used primarily to treat allergic reactions produced by the release of histamine e.g., edematous states, pruritus, allergic rhinitis and urticaria. They are generally more effective in acute conditions and are used only for symptomatic relief.

b) **Motion sickness:** Drugs like promethazine have value in prophylaxis of motion sickness.

c) **Antiparkinsonism:** Based on anticholinergic property, some H_1-antagonists such as diphenhydramine can be used in the early stages of treatment of parkinsonism.

d) **Local anesthetics:** In patients allergic to local anesthetics like procaine, the antihistaminc diphenhydramine have been used successfully as local anaesthetic.

7.4.2 Newer/Second Generation Antihistaminics

There are the agents which do not produce much sedation as side effects and are termed as second generation antihistaminics.

a) **Cetirizine**

Cetirizine is a potent antihistaminic with a low potential for drowsiness at pharmacologically active doses and with additional antiallergic properties. It is a selective H_1 antagonist with negligible effects on other receptors and is, therefore, virtually free from anti-cholinergic and anti-serotonin effects.

Cetirizine is **indicated** for the symptomatic treatment of perennial allergic rhinitis, seasonal allergic rhinitis, chronic idiopathic urticaria, conjunctivitis and pruritus in adults and children above two years of age.

b) **Fexofenadine**

It is a non-sedating antihistaminic with selective peripheral H_1 receptor antagonist activity. No sedative or other CNS effects were observed. Fexofenadine does not cross the blood-brain barrier.

7.4.3 H_2-Receptor Antagonists

As discussed earlier, H_2 receptors are responsible for histamine induced gastric acid secretion. H_2-receptors antagonists such as cimetidine, ranitidine, famotidine etc. are used in the treatment of peptic ulcer and are discussed in unit 'Antiulcer agents'.

SAQ 1

a) Smooth muscle contraction by histamine is mediated through _____ receptor.

b) Most common side effect, common to all H_1 antagonists is _____.

c) H_2 receptors are responsible for histamine induced _____.

7.5 SEROTONIN AND ITS ANTAGONISTS

7.5.1 5-Hydroxytryptamine (5-HT, Serotonin)

Serotonin is also known as 5-Hydroxytryptamine is widely distributed in plant and animal tissues, mast cells, platelets, the enterochromaffin cells located throughout the gastrointestinal tract (GIT), and in certain regions of the brain. It is also present in the venoms and stings. Some fruits such as bananas, pineapples, tomatoes and plums contain considerable amount of 5-HT.

It is formed in biological systems from the amino acid L-tryptophan by hydroxylation with tryptophan hydroxylase enzyme, followed by the decarboxylation by the nonspecific aromatic L-amino acid decarboxylase. 5-HT is then taken up into secretory granules and stored.

5-HT can directly stimulate or relax smooth muscles and can influence the release of noradrenaline from adrenergic nerves and stimulate endothelial cells to release prostaglandins. It acts directly to constrict the arteries and increases the peripheral vascular resistance. It increases the motility of the small intestine, stomach and also large intestine by which peristalsis is increased & diarrhoea can occur.

7.5.2 5-HT Antagonists

Many of the drugs are partial agonists or antagonise certain action of 5-HT but stimulate others. The two drugs that are usually classified as 5-HT antagonist namely methysergide and cyproheptadine is used as a potent $5\text{-}HT_1$ antagonist, while another drug, ketanserin is highly selective for blocking $5HT_2$ receptors. The important drugs are:

Methysergide

It antagonises the vasoconstrictor and pressor effect of 5-HT as well as the action of the amine on a variety of extravascular smooth muscles. It has been used for migraine prophylaxis, vascular headaches, to combat diarrhoea and malabsorption in carcinoid patients.

Cyproheptadine

It increases the appetite and promotes weight gain. It is used in controlling intestinal manifestations of carcinoid and postgastrectomy dumping syndrome.

Ketanserin

It blocks 5-HT induced vasoconstriction, platelet aggregation and contraction of airway smooth muscle. It is an effective antihypertensive, but the mechanism of action is not clear.

SAQ 2

a) Serotonin is formed in biological systems from the amino acid _____.

b) In the GIT, 5-HT is mostly present on the _____ cells.

7.6 PROSTAGLANDINS

In 1935, von Eular demonstrated a substance present in the extracts of human seminal fluid, which caused contraction of the isolated intestine and uterine muscle. This substance was named as 'prostaglandin' (PG) because of its probable origin from the prostate gland. In 1962, the structure of two prostaglandins namely PGE_1 & $PGF_{2\alpha}$ were elucidated and in 1964, PGE_2 was biosynthesized.

Prostaglandins are biologically active derivatives of 20 carbon atom polyunsaturated essential fatty acids, which contains 3, 4 or 5 double bonds (e.g. 5, 8, 11, 14 - eicosatetraenoic acid i.e. arachidonic acid). In human being, arachidonic acid is the most important precursor for the biosynthesis of eicosanoids.

7.6.1 Actions

The action of these agents on the various body organs is as follows:

Uterus: Uterine smooth muscles in pregnant women are uniformly contracted by PGF's. PGI_2 and high concentrations of PGE_2 produce relaxation. While, non-pregnant human uterus are contracted by PGF's but relaxed by PGE's.

Bronchial muscle: Bronchial and tracheal muscle are contracted by PGF's & PGD_2 and relaxed by PGE's. Asthmatic patients are sensitive to $PGF_{2\alpha}$.

Gastrointestinal tract: Longitudinal muscle is contracted by PGE_2 & PGF_{2alpha}, while circular muscle is contracted by PGI_2 & $PGF_{2\alpha}$ and relaxed by PGE_2. PGE's & PGI_2 also inhibit gastric acid secretion stimulated by gastrin or histamine.

Cardiovascular system: PGE's are potent vasodilators. However, PGF's constricts arterioles and veins. PGI_2 inhibits the aggregation of human platelets *in vitro*. TXA_2 is a very powerful inducer of platelet aggregation.

Endocrine system: Systemic administration of PGE_2 increases circulating concentration of ACTH, GH, prolactin & gonadotrophins.

7.6.2 Uses

Some of the important therapeutic uses of prostaglandins are as follows:

i) **Abortifacient:** Intra-amniotic administration of $PGF_{2\alpha}$ produced abortion with less severe adverse effects. It is used to induce second trimester abortion & usually administered as a single 40 mg intra-amniotic injection.

Synthetic PGE_2 analogues are also used as suppositories for abortion. It directly affects the collagenase of the cervix and also stimulates the contraction of the uterus.

ii) **Induction of labour:** PG's do not have any advantage over oxytocin for the induction of labour. The adverse effects of the prostaglandins are slightly higher than that produced by oxytocin. PGF_{2alpha} has more gastrointestinal toxicity than PGE_2 and is a bronchoconstrictor also. Oral PGE_2 is superior to oral oxytocin.

iii) **Peripheral vascular diseases:** Infusion or intra-arterial injection of prostacyclin (PGI_2) improves potency of blood vessels in certain peripheral vascular diseases. Infusion of PGI_2 can also reduce the infarct size in immediate post-myocardial infarction period.

iv) **Respiratory system:** PGE_2 is a powerful bronchodilator when given in aerosol form, but due to its irritant action on bronchial mucosa its clinical utility is limited.

v) **Renal system:** PGE_1, PGE_2 & PGI_2 increase glomerular filtration through their vasodilatory effects and increase water & sodium excretion.

vi) **Gastric ulcer:** PGE_2 & PGI_2 has been found to promote healing in gastric ulcer. PGE's are cytoprotective at low doses and inhibit gastric acid secretion at higher doses.

vii) PGE_1 (Alprostadil) is being used as IV infusion in infants with congenital heart defects, to maintain the potency of ductus arteriosus.

viii) Some of the prostaglandin analogues used clinically are: Misoprostol, Rioprostil, Enprostil, Arbaprostil, Trimoprostil, Dinoprostone, Carbacyclin, Iloprost, Dinoprost etc.

SAQ 3

a) Prostaglandins are biologically active derivatives of 20 carbon atom _____ acid.

b) _____ is used to induce second trimester abortion.

c) _____ is used as IV infusion in infants with congenital heart defects, to maintain the patency of ductus arteriosus.

7.7 SUMMARY

- Only drugs that block H_1 type of histamine receptors are called antihistaminics.
- The most important advantage of newer antihistaminics is that unlike the older generation compounds, sedation is less.
- In human being arachidonic acid is the most important precursor for the biosynthesis of prostaglandins.
- Most important clinical uses of prostaglandins are as an abortifacient, as an inducer of labour and in the treatment of gastric ulcers.

7.8 TERMINAL QUESTIONS

1. Classify antihistaminics. What are the advantages of newer compounds over first generation antihistaminics?
2. What are the therapeutic uses of antihistaminics?
3. What are the pharmacological actions of 5-HT?
4. Discuss the actions of prostaglandins.
5. Enumerate the therapeutic uses of prostaglandin analogues.

7.9 ANSWERS

Self Assessment Questions 1

1. a) H_1 b) Sedation c) Gastric acid secretion
2. a) L-tryptophan b) Enterochromaffin
3. a) Arachidonic b) $PGF_{2\alpha}$ c) PGE_1 (Alprostadil)

Terminal Questions

1. Antihistaminics are substances that block the action of histamine on H_1 receptors. They are Diphenhydramine, Pheniramine maleate, Promethazine and Cyclizine.

   The main advantage of second generation compounds over the first generation compounds is that they are less sedating and have less antimuscarinic actions.

2. H_1 antagonists have a widespread value in the symptomatic treatment of various disorders like:

   Hypersensitivity reactions: To prevent allergic reactions or to treat their symptoms, in which histamine is the primary mediator, the H_1-antagonists

are the drugs of choice and are often quite effective. They are used primarily to treat allergic reactions produced by the release of histamine e.g., edematous states, pruritus, allergic rhinitis and urticaria. They are generally more effective in acute conditions and are used only for symptomatic relief.

Motion sickness: Drugs like promethazine, promethazine chlorotheophyllinate, diphenhydramine, dimenhydrinate and cyclizine have value in prophylaxis of motion sickness.

Antivertigo: Drugs line cyclizine and diphenhydramine are used in the treatment of vertigo.

Antiparkinsonism: Based on anticholinergic property, some H_1-antagonists such as diphenhydramine can be used in the early stages of treatment of parkinsonism.

Local anesthetics: In patients allergic to procaine H_1-antagonists, such as diphenhydramine has been used successfully as local anaesthetic.

3. The main pharmacological actions of 5-HT are exerted on the cardiovascular system and smooth muscles in the body.

   5-HT can directly stimulate or relax smooth muscles via 5-HT_1 & 5-HT_2 receptors and can influence the release of noradrenaline from adrenergic nerves and stimulate endothelial cells to release EDRF and prostaglandins. It acts directly to constrict the arteries and increases the peripheral vascular resistance.

   5-HT stimulates smooth muscles, it increases the motility of the small intestine, stomach and also large intestine by which peristalsis is increased & diarrhoea can occur.

4. The pharmacological actions of prostaglandins on various body systems are enumerated as follows:

   Uterus: Uterine smooth muscles in pregnant women are uniformly contracted by PGF's. PGI_2 and high concentrations of PGE_2 produce relaxation. While, non-pregnant human uterus are contracted by PGF's but relaxed by PGE's.

   Bronchial muscle: Bronchial and tracheal muscle are contracted by PGF's & PGD_2 and relaxed by PGE's. Asthmatic patients are sensitive to $PGF_{2\alpha}$ and PGE_1 & PGE_2 causes bronchodilatation

   Gastrointestinal tract: Longitudinal muscle is contracted by PGE_2 & PGF_{2alpha}, while circular muscle is contracted by PGI_2 & $PGF_{2\alpha}$ and relaxed by PGE_2. PGE's & PGI_2 also inhibit gastric acid secretion stimulated by gastrin or histamine.

   Cardiovascular system: PGE's are potent vasodilators. However, PGF's constricts arterioles and veins. PGI_2 inhibits the aggregation of human

platelets *in vitro*. TXA_2 is a very powerful inducer of platelet aggregation. LTB_4 stimulates the aggregation of polymorphonuclear leukocytes.

Endocrine system: Systemic administration of PGE_2 increases circulating concentration of ACTH, GH, prolactin & gonadotrophins.

5. The therapeutic uses of prostaglandin analogues have been enumerated below:

Abortifacient: Intra-amniotic administration of $PGF_{2\alpha}$ produced abortion with less severe adverse effects. It is used to induce second trimester abortion & usually administered as a single 40 mg intra-amniotic injection. Synthetic PGE_2 analogues are also used as suppositories for abortion. It directly affects the collagenase of the cervix and also stimulates the contraction of the uterus.

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