Lecture title: Autacoids

Lecturer Affiliation: College of Veterinary Medicine

Summary:

Autacoids

Autacoids are chemical mediators that are synthesized and their function in a localized tissue and participate in physiologic or pathophysiologic responses to injury. They act locally and therefore also termed "local hormone. Autacoids are short-lived and rapidly degraded.

Major classes.

1. Decarboxylated amines:

- Histamine
- serotonin (5-hydroxytryptamine)

2. Polypeptides:

- Bradykinin
- Angiotensin
- Vasopressin
- Atrial natriuretic peptide
- Vasoactive intestinal polypeptide
- Substance P

3. Lipid-derived: Eicosanoids. Prostaglandins, leukotrienes, thromboxane

4. Cytokines

Histamine

Histamine is an amine formed by the decarboxylation of the amino acid histidine by the enzyme histidine decarboxylase.

Storage:

1.Tissues:

It is found in all tissues but is present in high concentrations in the lungs, skin, and GIT.

2.Cells:

Mast cells and basophiles

3.Neurons:

Histaminergic neurons in the brain

	location	Pharmacological effects
H1	1.**CNS**	Increase Ach and glutamate (excitatory NT)
	2.**Smooth muscle**	• Contraction in all smooth m. **except** in blood vessels • vasodilation (H1) H1→ ↑NO production →VD • increase capillary permeability via H1 → edema
	3.**Excocrine gland**	Increase secretion in all these glands like lacrimal g. , bronchial g, salivary g. , gastric gland and nasal gland .
	4.**Nerve ending**	Itching and pain
H2	**1. Stomach** **2. Heart** **3. Mast cell**	Increase HCL Increase contractility Feedback mechanism
H3	1-**Presynaptic neurons** 2-**CNS**	Decrease release of NT (H, Ach, NE and 5HT)

H4	**Immune cell**	Mast cell chemotaxis and leukotriene B4 production (↑)

Receptors of histamine

Histamine antagonist

1-Physiological antagonist (Adrenaline).

2-Histamine receptor blocker (antihistamines).

3- Inhibition of histamine release

a- Mast cell stabilizers: Cromolyn Na, Nedocromil and ketotifen

b- Beta2 agonist e.g. salbutamol

c- Methyl-Xanthine (PDE inhibitor e.g. theophylline)

4- Corticosteroids: Cortisone

5- Histaminase enzyme (Di-amine Oxidase): responsible for metabolizing increased level of H.

Histamine antagonisms

1. Physiologic antagonists to histamine.

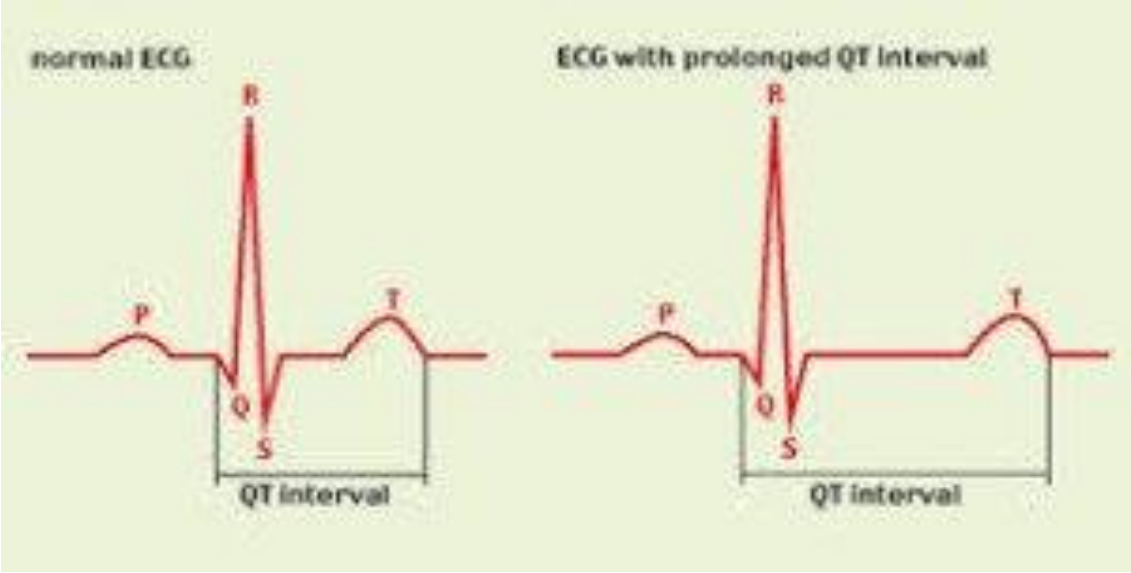
Epinephrine, phenylephrine and ephedrine antagonize the actions of histamine by antagonizing histamine's physiological function.

2. Histamine receptor blocker (Antihistamines).

H1-antihistamines

First generation	Second generation
• **Diphenhydramine** • Dimenhydrinate • Hydroxyzine • Chlorpheniramine • Meclizine • Promethazine • Doxylamine • **Cyproheptadine**	• **Loratadine** • Cetirizine • Ketotifen • Levocetirizine • Desloratadine
MOA: act as competitive antagonists of H_1, α_1, 5HT and M_3 receptors	**MOA:** act as competitive antagonists of peripheral H_1, receptors only.
Cross BBB	NOT Cross BBB

Lipophilic	Hydrophilic
Have sedation effect	No
Less potent	More potent
Short duration	Long duration
The side effect its sedation	The side effect is prolonging Q T Interval



Therapeutic uses:

1- Treatment of patients with *allergic conditions*

(a) Urticaria and pruritus

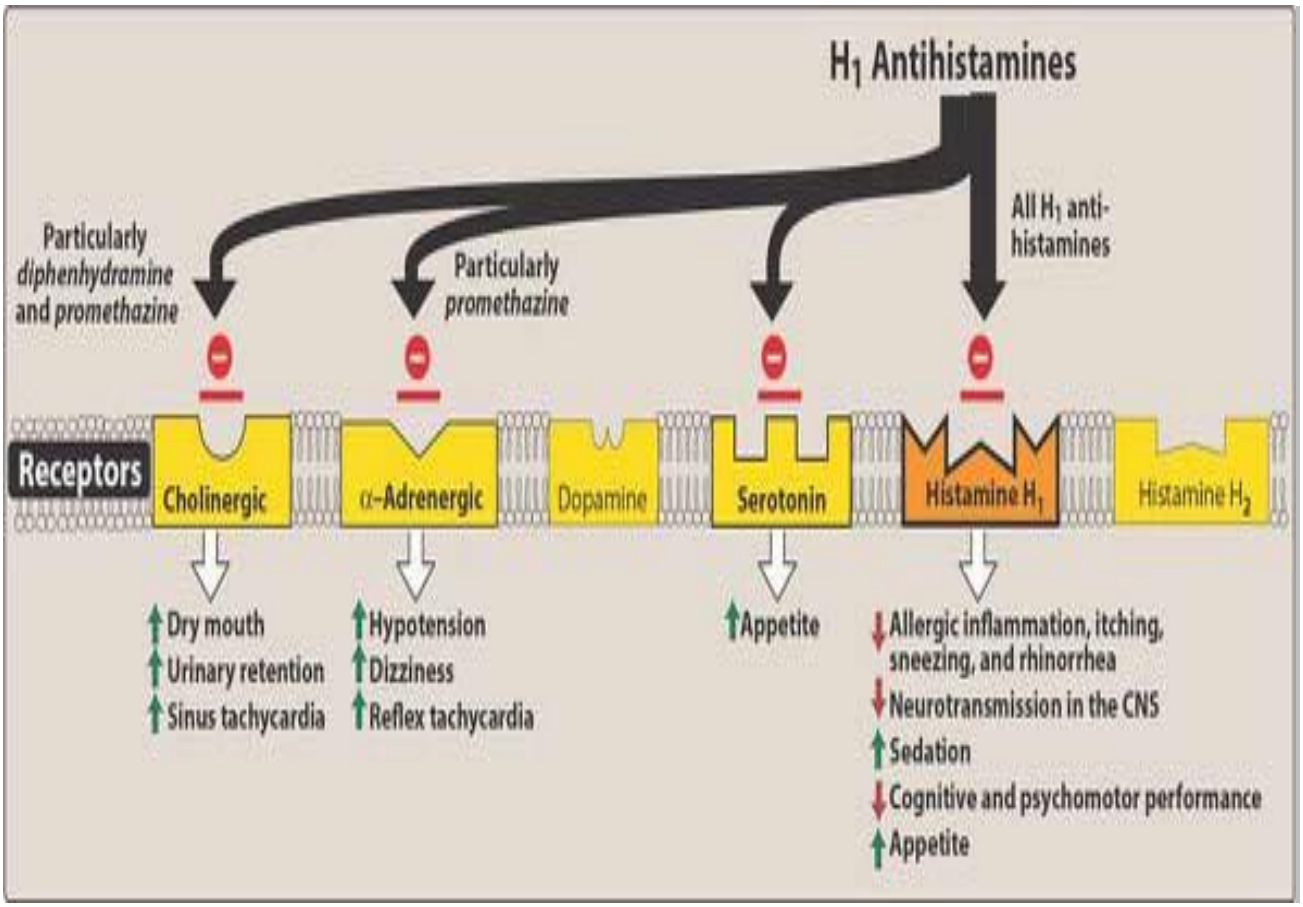
(b) Allergic reactions to drugs

(c) Anaphylaxis

2- Prevention of motion sickness.

Diphenhydramine, dimenhydrinate, and meclizine

3- Sedation and hypnotic :Doxylamine have strong sedative effect.



H2-antihistamines.

These drugs are inhibitors of gastric acid secretion.

-Cimetidine

-Ranitidine

-Famotidine

-Roxatidine

Mechanism of action

H2-antihistamines competitively inhibits (H2-receptors) in parietal cell and thereby decreases gastric acid production during basal conditions and when stimulated by food, vagal activity, pentagastrin, gastrin, or histamine.

Therapeutic uses:

- Equine gastric ulcers.
- *Cimetidine is least potent among the four H2-antihistamines. Lack of therapeutic effect of cimetidine has been reported in dogs.*

Drug interactions. Cimetidine can **inhibit the hepatic cytochrome P450 enzymes**. It may reduce the metabolism of other drugs, which undergo hepatic metabolism, thereby elevating and prolonging their concentration in the plasma.

Adverse effect of cimetidine: cimetidine inhibits binding of dihydrotestosterone to androgen receptors (**anti- androgenic effect**) and increase serum prolactin cause →

- Gynecomastia in male ‘
- Impotence in male
- Galactorrhea in female

Mast cell stabilizer:

Cromolyn sodium, ketotifen

Cromoglicate inhibits degranulation of mast cells and release of histamine and other autacoids, Cromoglicate may act by inhibiting calcium influx. It is not well absorbed from the gut and has no clinical use when given orally.

Therapeutic uses

(1) Pulmonary and nasal allergic reactions.

(2) It is used in a prophylactic manner.

(3) It has been used in the horse where it is nebulized and delivered via a face mask.

(4) The 4% eye drop is used to control allergic conjunctivitis.