Histamine and Antihistaminics

Autacoids

These are diverse substances **produced by wide variety of cells**, having **intense biological activity**, but **act locally** at the site of synthesis and release

➢ **Types of autacoids:**

- **Amine autacoids**
  - Histamine, 5-HT (Serotonin)
- **Peptide autacoids**
  - Plasma kinins (Bradykinin, Kallidin), Angiotensinogen
- **Lipid autacoids**
  - Prostaglandins, Leukotrienes, PAF

Histamine - Introduction

is an endogenous substance synthesized, stored and released in

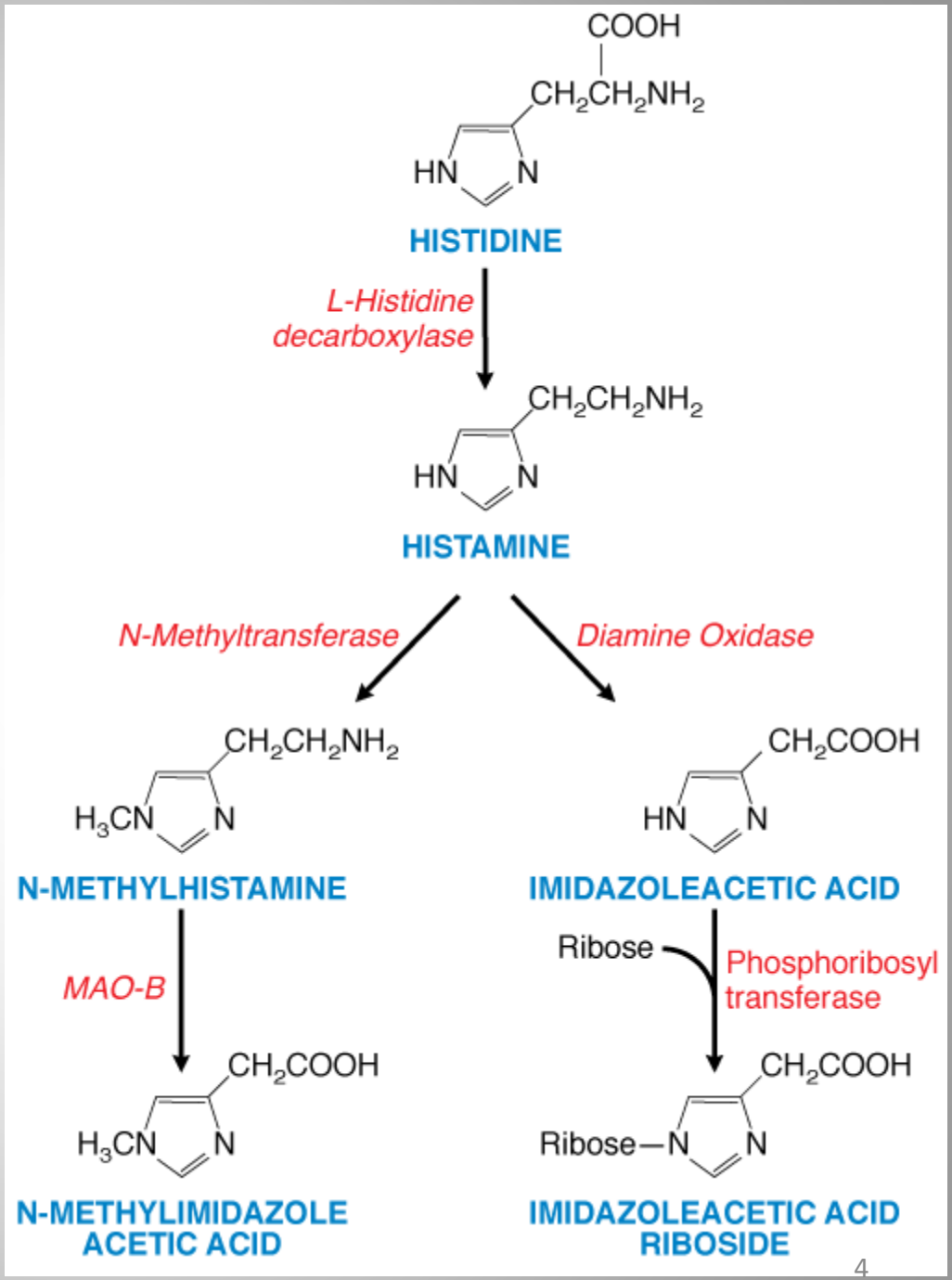
(a) *mast cells*, which are abundant in the skin, GI, and the respiratory tract,

(b) *basophils* in the blood, and

(c) some *neurons* in the CNS and peripheral NS

Synthesis & Storage

- Histamine is formed by the decarboxylation of the amino acid histidine by the enzyme L-histidine decarboxylase, found in every mammalian tissue that contains histamine.
- These cells synthesize histamine and store it in secretory granules.



The different Histamine receptors

	Location	Effect	Treatment
H1	1 -smooth muscles •2-vascular endothelial cells:Vasodilatation •Of small BV •-Smooth muscle of large vessels-vasoconstriction 3-CNS:+Ach - +glutamat - 4-excocrine glands:salivary,lacrymal, GIT	Mediate an increase in vascular permeability at sites of inflammation induced by histamine	Allergies
H2	-gastric parietal cells -heart -negative feedback release of histamine.	Increases the release of gastric acid	Stomach ulcers
H3	Found mostly in the CNS:antagonise action of H1:-ve feedback	Neural presynaptic receptor, may function to release histamine	Unknown:sleep awake cycle.
H4	chemotaxis	Unknown	treatment of autoimmune diseases. (rheumatoid arthritis

Histamine – The Triple Response

Subdermal histamine injection causes:

1. Red spot (few mm) in seconds: direct vasodilation effect , H1 receptor mediated
2. Flare (1cm beyond site): axonal reflexes, indirect vasodilation, and itching, H1 receptor mediated
3. Wheal (1-2 min) same area as original spot, edema due to increased capillary permeability, H1 receptor mediated

Pharmacological actions

Heart :

- It increases the force of contraction of both atrial and ventricular muscle

Due to H_2 receptors

- Slowed AV conduction (-ve dromotropic effect) which involves mainly H_1 receptors

-- blood pressure

Pharmacological actions

- **Visceral Smooth Muscles**
  - **Bronchoconstriction**
  - **Abd. Cramps & colic**
- **Glands**
  - **↑ in gastric secretion**
- **Sensory nerve endings**
  - **IV – itching , Pain**

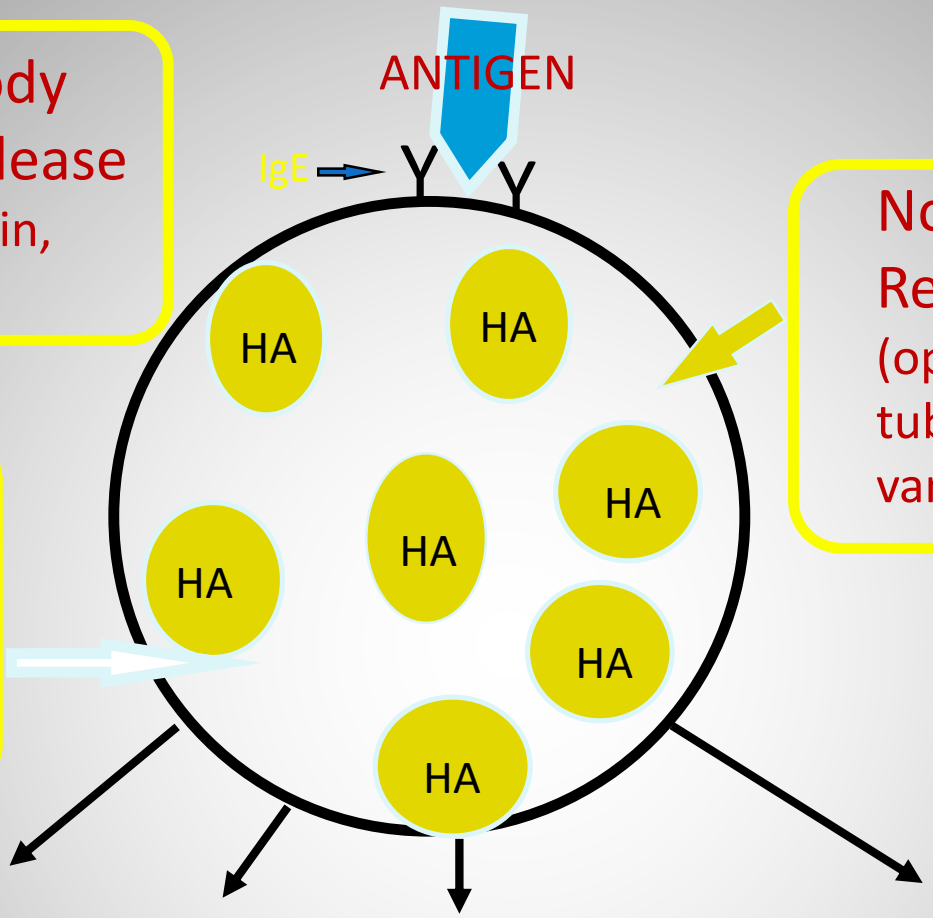
Pathophysiological roles

- Cellular mediator of immediate hypersensitivity reaction and acute inflammatory response
- Anaphylaxis
- Seasonal allergies
- Duodenal ulcers
- Gastrinoma (Zollinger-Ellison Syndrome)

IgE - Antibody Induced Release (food, penicillin, venoms, etc)

Inhibitors of Release (Cromolyn, Albuterol)

Non-immune Releasers (opioids, tubocurarine, vancomycin etc)



PGs & LTs PROTEASES HISTAMINE OTHER MEDIATORS (PAF,TNF,ILs)

ACUTE INFLAMMATORY RESPONSE
IMMEDIATE HYPERSENSITIVITY REACTION

Antagonists of Histamine

- **Physiological antagonists :**

  Adrenaline – effects are opposite to effects of histamine

- **Histamine release Inhibitors :**

  Mast cell stabilizers : Cromoglycate

- **Histamine receptor blockers :**

  H1 blockers and H2 blockers

H_1-RECEPTOR ANTAGONISTS

- **1st Generation:**
  - **Highly sedatives:** Diphenhydramine, Dimenhydrate
  - **Moderately:** Cyproheptadine, Meclizine and Cinnarizine
  - **Mild:** Chlorpheniramine, Cyclizine, Clemastine
- **2nd Generation:** Fexofenadine, Loratidine

CHART 4: Differences between first and second-generation H1 antihistamines

First-generation H1 antihistamines	Second-generation H1 antihistamines
Usually administered in three to four daily doses	Usually administered once or twice a day
Cross the blood-brain barrier (lipophilicity, low molecular weight, lack of recognition by the P-glycoprotein efflux pump	Do not cross the blood-brain barrier (lipophobicity, high molecular weight, recognition by the P-glycoprotein efflux pump)
Potentially cause side-effects (sedation/ hyperactivity/insomnia/convulsions)	Do not cause relevant side-effects (sedation/fatigue/hyperactivity/convulsions), in the absence of drug interactions
Case reports of toxicity are regularly published	No reports of serious toxicity
No randomized, double-blind, placebo-controlled trials in children	Some randomized, double-blind, placebo-controlled studies in children
Lethal dose identified for infants/young children	Do not cause fatality in overdose

Adapted source: de Benedictis FM, et al [26]

Antihistaminics (Pharmacokinetics)

- **Absorption:** Antihistaminics (H_1 receptor antagonists) are well absorbed from oral and parenteral routes
- **Distribution:** widely in the body and enter brain. Newer compounds penetrate the brain poorly.
- **Metabolism:** In liver
- **Excretion:** In urine

Pharmacological Actions

- CNS depression: (More with first generation)
  - Sedation and drowsiness
  - Some have antiemetic and antiparkinsonian effects
- Antiallergic action: Type- I reactions are suppressed
- Anticholinergic actions (More with first generation)
  - Dryness of mouth , Blurring of vision
  - Constipation
  - Urinary retention

Pharmacological Actions

- **BP**

-Fall in BP with IV injection (all) but not with Oral

- direct smooth muscle relaxation or α adrenergic blockade
- **Antagonism of Histamine**
  - Effectively block:
    * Bronchoconstriction
    * Contraction of sm. Mus.
    * Triple response

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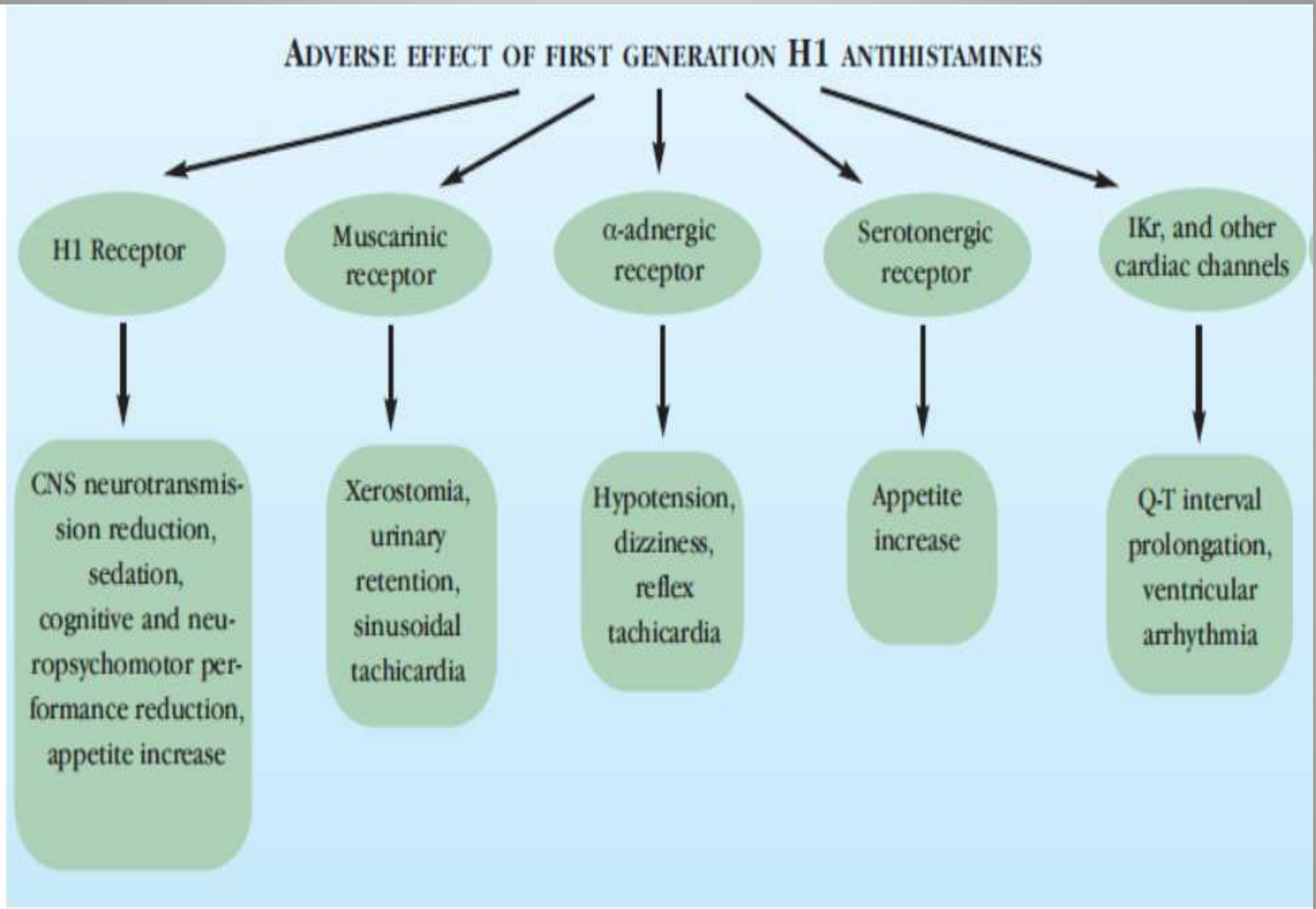

FIGURE 5: Symptoms and signs of the adverse effects of first-generation H1 antihistamines

Second Generation Agents

Adverse effects:

have a much lower incidence of adverse effects than the first generation agents.

- terfenadinand astemizole were removed from the market due to effects on cardiac K+ channels - prolong QT interval (potentially fatal arrhythmia *"torsades de pointes"*)
- Cetirizine appears to have more CNS actions (sedative)
- Erythromycin and ketoconazole inhibit the metabolism of fexofenadine and loratadine in healthy subjects, this caused no adverse effects.

Pharmacological Actions

- Antimotion sickness effect
- Antiemetic
- Antiparkinsonism
- Antivertigo

Antihistaminics (Uses)

- Allergic disorders,
- Other conditions involving histamine: Insect bite, Ivy poisoning etc.
- Common cold
- Motion sickness
- Vertigo
- Pre anesthetic medication
- Cough
- Parkinsonism
- As sedative, hypnotic, anxiolytic

H_2 receptor antangnists

- **Cimetidine , Ranitidine, Famotidine**

Clinical uses-

- Peptic Ulcer and Duodenal Disease
- Gastric Ulcer: reduce symptoms promote healing for benign gastric ulcers
- Gastroesophageal Reflux Disorder (erosive esophagitis**)** Hypersecretory Disease:
- Zollinger-Ellison syndrome: acid hypersecretion -- caused by gastrin-secreting tumor

THANK YOU