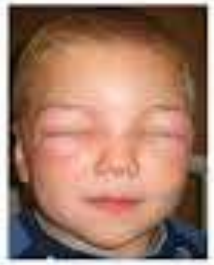
Histamine & Histamine Antagonists

Histamine:

- It is not a drug but is important due to its physiological and pathophysiological actions. Therefore, drugs that inhibit its release or block its receptors have therapeutic value.
- is an endogenous substance synthesized, stored and released in
  (a) mast cells, which are abundant in the skin, GI, and the respiratory tract,
  (b) eosinophils in the blood, and
  (c) some neurons in the CNS and peripheral NS

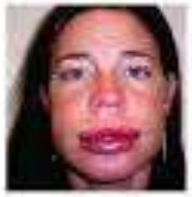
Pathophysiological Actions of Histamine

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



Angioedema

Urticaria



Synthesis and Metabolism

- **1) Synthesized in the cell from L-histidine**

L-histidine -----*L-histidine decarboxylase*----→ Histamine

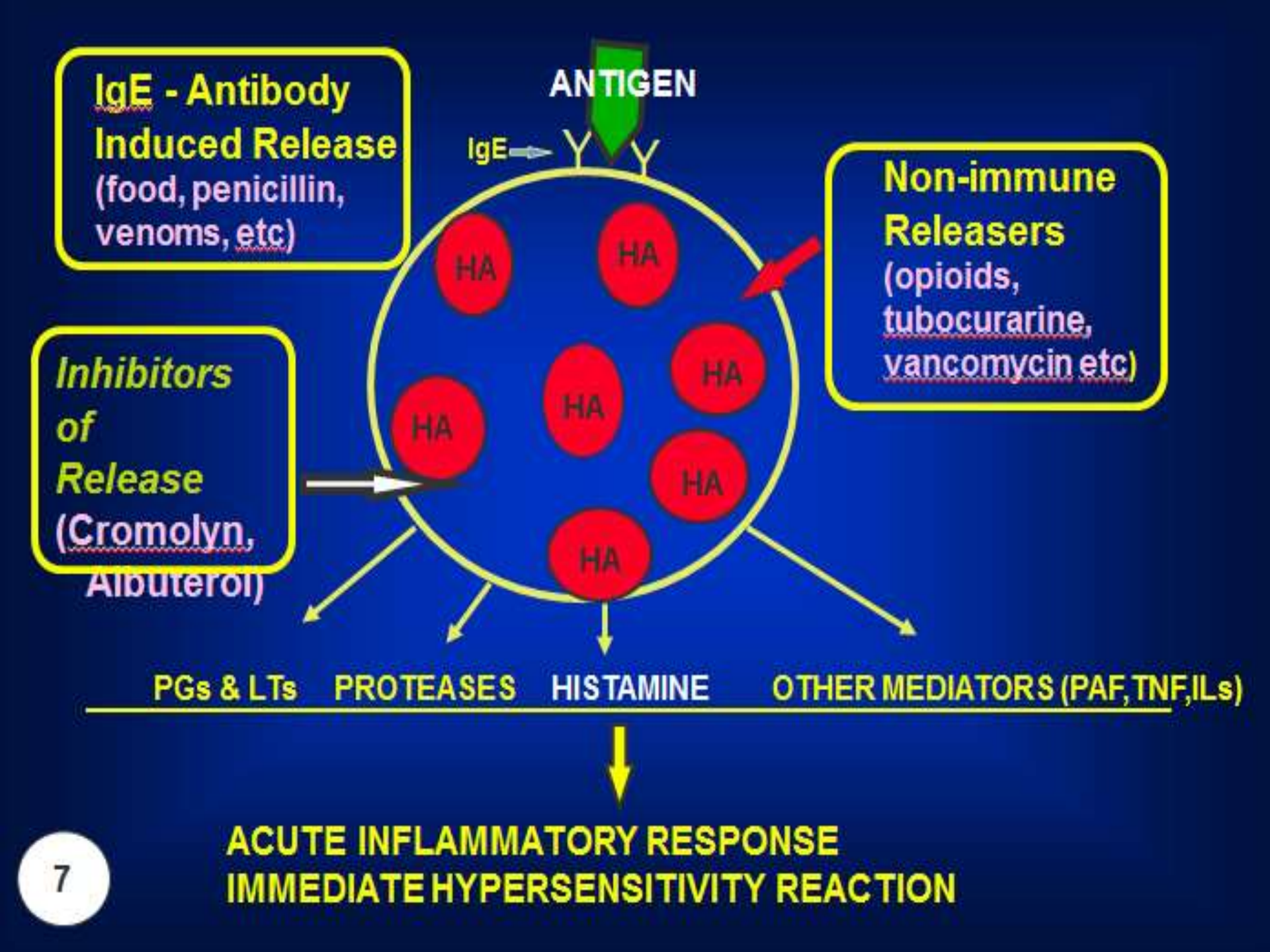
- **2) Metabolized by P450 system, 2 pathways:**
- **Methylation to N-me histamine (*N-me transferase*), and to N-me imidazole acetic acid (*MAO*) - eliminated in urine**
- **Oxidative deamination to imidazole acetic acid (*DAO*), and to imidazole acetic acid riboside - eliminated in urine**

IgE - Mediated Releasers

- **Food**: eggs, peanuts, milk products, grains, strawberries, etc
- **Drugs**: penicillins, sulfonamides, etc
- **Venoms**: fire ants, snake, bee, etc
- **Foreign proteins**: nonhuman insulin, serum proteins, etc

Non-immune Releasers

- Morphine and other opioids, i.v.
- Aspirin and other NSAIDs in some asthmatics
- Vancomycin, i.v. (Red man syndrome), polymixin B
- Some x-ray contrast media
- Succinylcholine, tubocurarine


IgE - Antibody Induced Release (food, penicillin, venoms, etc)
ANTIGEN
IgE
HA
HA
HA
HA
HA
HA
HA
Non-immune Releasers (opioids, tubocurarine, vancomycin etc)
Inhibitors of Release (Cromolyn, Albuterol)
PGs & LTs
PROTEASES
HISTAMINE
OTHER MEDIATORS (PAF, TNF, ILs)
ACUTE INFLAMMATORY RESPONSE
IMMEDIATE HYPERSENSITIVITY REACTION

Clinical Symptoms Associated With Histamine Release

- mild/cutaneous
  - erythema, urticaria, and/or itching
- mild to moderate
  - skin reactions, tachycardia, dysrhythmias, moderate hypotension, mild respiratory distress
- severe/anaphylactic
  - severe hypotension, ventricular fibrillations, cardiac arrest, bronchospasm, respiratory arrest

Receptors: Distribution and Function

- **H1 – Smooth muscle, endothelium, CNS. Bronchoconstriction, vasodilation, separation of endothelial cells, pain and itching, allergic rhinitis, motion sickness.**
- **H2 – gastric parietal cell, vascular s.m. cell, basophils. Regulate gastric acid secretion, It also has a cardiac stimulant effect. A third action is to reduce histamine release from mast cells—a negative feedback effect.**
- **H3 - CNS cells, and some in peripheral NS. Presynaptic, feedback inhibition of histamine synthesis and release.**
- **H4 - Highly expressed in bone marrow and white blood cells. Mediate mast cell chemotaxis**

Triple Response of Lewis

Subdermal histamine injection causes:

Dermatographia

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

Histamine H1- Antagonists

- First Generation:
- Sedating

- Second Generation:
- Nonsedating

First Generation Agents

- ***Examples***

- **Ethanolamines: Diphenhydramine (Allermine)**
  Clemastine (Tavagyl)
- **Dimethindene (Fenistil)**
- **Ethylenediamine: Triprolidine (Actifed)**
- **Alkylamine: Chlorpheniramine (Histadin)**
- **Phenothiazine: Promethazine (Phenergan)**
- **Piperazines: Hydroxyzine (Atarax)**
  Cyclizine ; Meclizine (Antivert)

First Generation Agents

- **Uses:**
- **Adjunctive in anaphylaxis and other cases where histamine release can occur (H2 antagonist, and epinephrine must also be used in anaphylaxis)**
- **Antiallergy (allergic rhinitis, allergic dermatoses, contact dermatitis)**
- **Sedative/sleep aid (Diphenhydramine)**
- **To prevent motion sickness (meclizine, cyclizine)**

- ***Uses (cont'd)***
- ***Antiemetic*: prophylactic for motion sickness (promethazine)**
- ***Antivertigo* (meclizine) safe in pregnancy**
- ***Local anesthetic*: (diphenhydramine)**
- ***Antitussive* (diphenhydramine)**

First Generation Agents

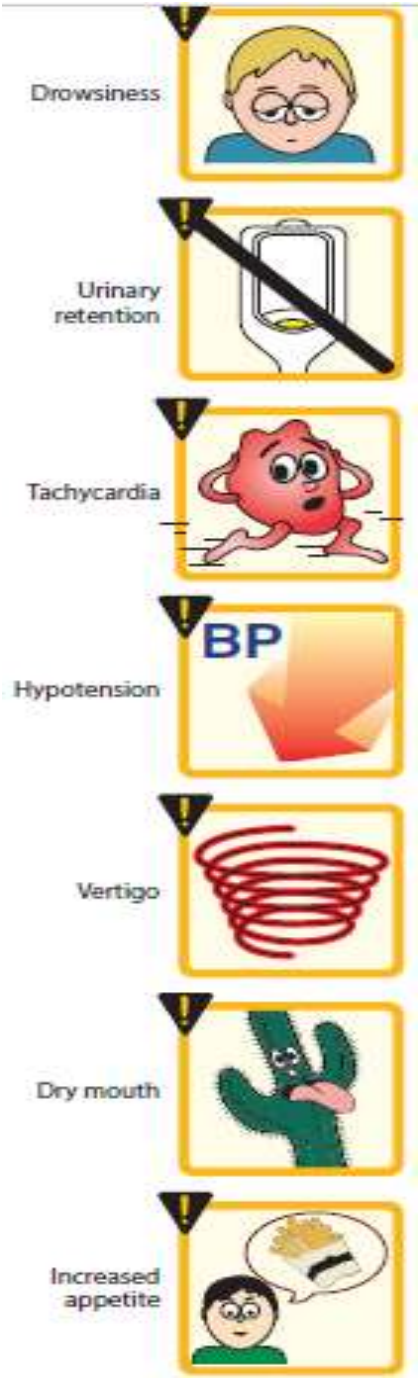
- ***Adverse Effects:***
- **Sedation** ***(Paradoxical Excitation***
- ***in children)***
- **Dizziness**
- **Fatigue**
- **Tachydysrhythmias** ***in overdose - rare***
- **Allergic reactions** ***with topical use***
- **Peripheral antimuscarinic effects**

➢ ***dry Mouth***

➢ ***blurred Vision***

➢ ***constipation***

➢ ***urinary Retention***



First Generation Agents

- ***Drug interactions:***
- ***Additive with classical antimuscarinics***

- ***Potentiate CNS depressants***

❖**opioids**

❖**sedatives**

❖**general and narcotic analgesics**

❖**alcohol**

First Generation Agents

- ***Pharmacokinetics:***
- ***All H1 blockers are active by the oral route. Several are promoted for topical use in the eye or nose.***
- ***Cross BBB and placenta***
- ***Most are metabolized extensively in the liver (induce hepatic microsomal enzymes).***
- ***Half-lives of the older H1 blockers vary from 4 to 12 h.***

Second Generation Agents

- ***Examples*** ***Uses***
- **Cetirizine (*Zyrtec*)** ***Antiallergy***
- **Fexofenadine (*Tel-fast*)**
- **Loratadine (*Clarinase*)**
- **Desloratadine (*Aerius*)**
- **Azelastin (*Intranasal Spray*)**

Second Generation Agents

- ***Adverse effects:***
- **in general, these agents have a much lower incidence of adverse effects than the first generation agents.**

- **terfenadine (seldane) and astemizole (hismanal) were removed from the market due to effects on cardiac K+ channels - prolong QT interval (potentially fatal arrhythmia "*torsades de pointes*")**

- **fexofenadine is active metabolite of terfenadine**

Second Generation Agents

- ***Adverse effects:***
- **Cetirizine appears to have more CNS actions (sedative) than fexofenadine or loratadine. recommended that cetirizine not be used by pilots.**

- **Erythromycin and ketoconazole inhibit the metabolism of fexofenadine and loratadine in healthy subjects, this caused no adverse effects.**

Second Generation Agents

- ***Pharmacokinetics:***
- **Cetirizine , loratadine , fexofenadine**

well absorbed and are excreted mainly unmetabolized form.

- **They are less lipid soluble than the first-generation agents**
- **Have half-lives of 12–24 h.**
- **They induce Cyt P450 liver enzymes**

HISTAMINE H2 ANTAGONISTS

A. *Classification and Prototypes*

- **Four H2 blockers are available; cimetidine**

(Tagamet)is the prototype.

- **Ranitidine (Zantac), famotidine, and nizatidine differ only in having fewer adverse effects than cimetidine.**
- **They are orally active, with half-lives of 1–3 h.**
- **All four agents are available in oral over-the counter formulations.**

Clinical Use

- **In acid-peptic disease, especially duodenal ulcer, these drugs reduce nocturnal acid secretion,**
- **Intravenous H2 blockers are useful in preventing**

gastric erosions and hemorrhage that occur in stressed patients in intensive care units.

- **In Zollinger-Ellison syndrome, which is associated with gastrinoma and characterized by acid hypersecretion, peptic ulceration, gastrointestinal bleeding, and diarrhea, but very large doses are required; proton pump inhibitors are preferred.**
- **Used in gastroesophageal reflux disease**

(GERD), but they are not as effective as proton pump inhibitors