HISTAMINE AND ANTIHISTAMINIC AGENTS

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Autacoids

- Greek: *autos* – self and *akos* - healing substance or remedy
- Diverse substances, produced by a wide variety of cells – generally act locally
- Also called local hormones – but differs from them
- A number of Physiological and pathological processes and also transmitters to Nervous system
- Amine Autacoids: **Histamine** and Serotonin
- Lipid derived: PG, LT and PAF
- Peptides: Plasma kinins and Angiotensin

Histamine - Introduction

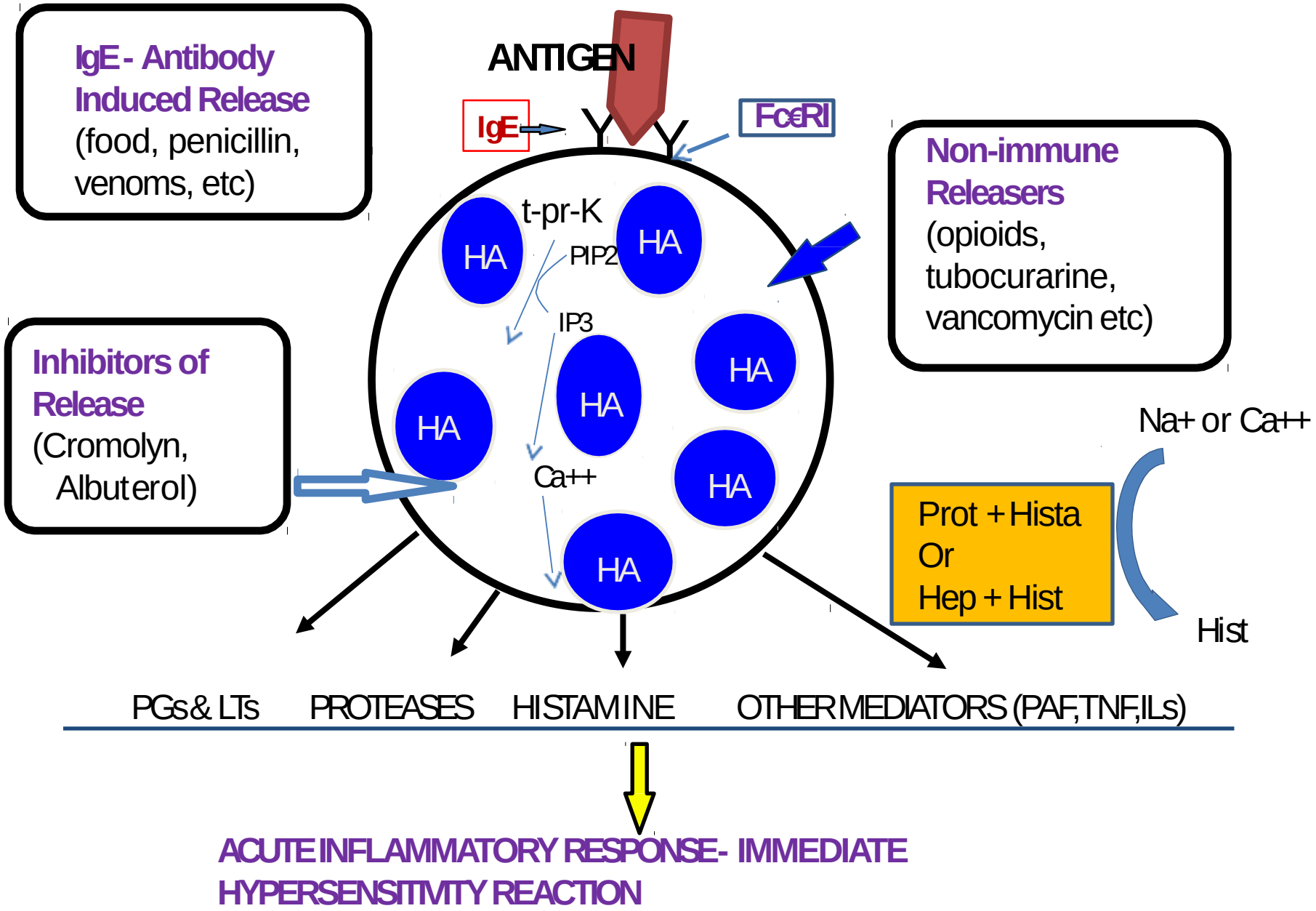
- Meaning “tissue amine” (*histos* – tissue) – abundantly present in animal tissues – also in plants like “stinging nettle”
- Mediator of hypersensitivity and tissue potential tissue injury – Physiological role
- The primary site the mast cell granules (or basophils)– skin, intestinal and gastric mucosa, lungs, liver and placenta
- Other sites
  - central nervous system: neurotransmitter
  - the fundus of the stomach: major acid secretagogues, epidermis, gastric mucosa and growing regions
  - also blood, body secretions, venoms & pathological fluids

Histamine – synthesis, storage and release

- Synthesized locally from amino acid histidine
- Histidine —*L-histidine decarboxylase*→ Histamine
- 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
- In mast cells – held by acidic protein and heparin (-ve charged) – histamine is +ve charged
- Ineffective orally – liver destroys all absorbed from intestine

Histamine Receptors

	H_1	H_2	H_3
Selective agonist	2-Methylhistamine	4-Methylhistamine	α-Methylhistamine
Selective antagonist	Mepyramine	Cimetidine Ranitidine	Thioperamide
Effector Pathway	IP_3/DAG	cAMP	Ca++ influx K+ channel activation
Distribution	•Smooth muscle (intestine, airway, uterus •Blood vessels – NO and PGI2 release – Vasodilatation and also vasoconstriction • Afferent nerves – stimulation •Ganglion cells – stimulation •Adrenal medulla – CA release •Brain - transmitter	•Gastric glands – acid secretion •Blood vessels – dilatation •Heart: Atria: + chronotropy and ventricles: + inotropy •Uterus – relaxation •Brain - transmitter	•Brain – inhibition oh Histamine release •Lung, spleen, gatric mucosa – decrease release •Ileum – inhibition of Ach release •Cerebral vessels – NA release inhibition


IgE - Antibody Induced Release
(food, penicillin, venoms, etc)
ANTIGEN
IgE
FcεRI
Non-immune Releasers
(opioids, tubocurarine, vancomycin etc)
t-pr-K
PIP2
IP3
Ca++
HA
Inhibitors of Release
(Cromolyn, Albuterol)
Na+ or Ca++
Prot + Hista
Or
Hep + Hist
Hist
PGs & LTs
PROTEASES
HISTAMINE
OTHER MEDIATORS (PAF, TNF, ILs)
ACUTE INFLAMMATORY RESPONSE- IMMEDIATE HYPERSENSITIVITY REACTION

Releasing Agents

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
- Enzymes: chymopapain

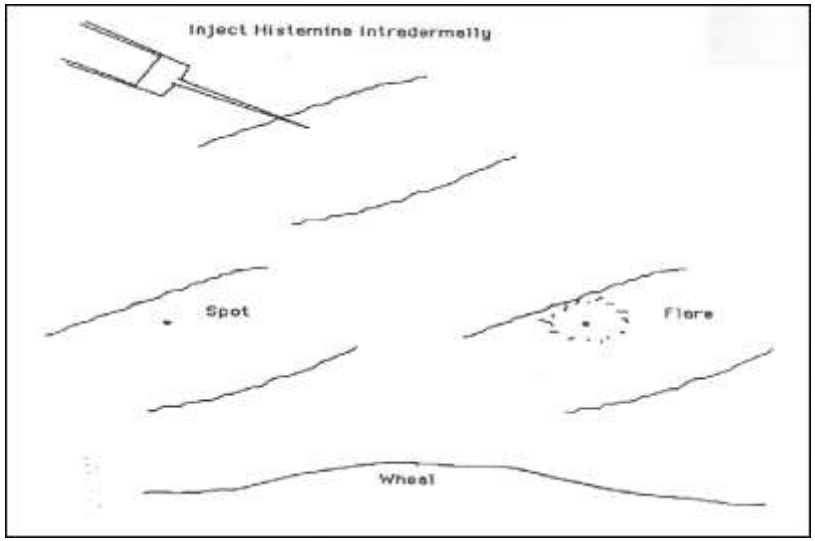
Non-immune Releasers

- 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, d-tubocurarine
- Anaphylotoxins: c3a, c5a
- Cold or solar urticaria

Histamine - Pharmacological actions

- Blood vessels: Dilatation of small vessels – arterioles, capillaries and venules
  - SC administration – flushing, heat, increased HR and CO – little fall in BP
  - Rapid IV injection: Fall in BP early (H_1) and persistent (H_2) – only H_1 effect with low dose
  - Dilatation of cranial vessels
  - H_1 component vasodilatation – mediated indirectly by EDRF.. But H_2 component - mediation is directly on smooth muscle of blood vessels
  - Larger arteries and veins – constriction mediated by H_1 receptor
  - Increased capillary permeability – exudation of plasma

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

- Affects both cardiac contractility and electrical events directly
  - It increases the force of contraction of both atrial and ventricular muscle by promoting the influx of Ca^{2+}, and
- Increased heart rate by hastening diastolic depolarization in the sinoatrial (SA) node
- It also acts directly to slow atrioventricular (AV) conduction, to increase automaticity, and in high doses especially - to elicit arrhythmias.
- With the exception of slowed AV conduction, which involves mainly H_1 receptors ----- all these effects are largely attributable to H_2 receptors and cAMP accumulation
- If histamine is given i.v., direct cardiac effects of histamine are overshadowed by baroreceptor reflexes elicited by the reduced blood pressure
- Overall: H_1 – decreased AV conduction; H_2 - Increased Chronotropy and automaticity

Pharmacological actions – contd.

- Visceral smooth muscles: Bronchoconstriction, intestinal contractions increased (colic), Uterus not affected
- Glands: Gastric secretion (also pepsin) – H_2 receptor mediated – cAMP generation and proton pump activation
- Sensory Nerve endings: Itching on injected; High doses – pain
- Autonomic ganglia and Adrenal Medulla: Adrenaline release – As a result **rise in Blood Pressure**
- CNS: Does not cross BBB – no CNS effects on IV
  - intracerebral injection: Rise in BP, Cardiac stimulation, hypothermia, arousal, vomiting

Histamine - Pathophysiological Roles

- **Gastric Secretion:** Dominant Physiological Role – Non-mast cell histamines – Gastric mucosa
  - All components involve to release it – feeding, vagal, cholinergic and gastrin
  - H_2 blockers – Suppress the release – antimuscarinics reduce the effects of Histamine

- **Allergic Phenomena:** First Role – mediation of hypersensitivity reactions
  - AG:AB reactions released by mast cells involving IgE types
  - Urticaria, angioedema, brochoconstriction and anaphylactic reaction
  - Antihistaminics – counter above effects except Brochial asthma

- **Transmitter:** Afferent transmitter – itch and pain

  Non-mast cell histamines - maintain wakefulness (midbrain and hypothalumus) .. antihistaminics cause sedation) …. also suppress appetite, regulates body temperature, thirst and hormone release from anterior pituitary

- **Inflammation:** Vasodilatation in inflammation and adhesion of leucocytes

H_1-RECEPTOR ANTAGONISTS

- Physiological antagonism (e.g., epinephrine)
- Inhibit the release of histamine(e.g., cromolyn
- Pharmacological antagonism (antihistamines)

First Generation:

Sedating

Second Generation:

Nonsedating

Classification

- **1st Generation:**
  - Highly sedatives: Diphenhydramine, Dimenhydrate, Promethazine and Hydroxyzine
  - Moderately: Pheniramine, Cyproheptadine, Meclizine, Buclizine and Cinnarizine
  - Mild: Chlorpheniramine, Dexchlorpheniramine, Dimethindene, Cyclizine, Clemastine
- **2nd Generation:** Fexofenadine, Loratidine, Desloratidine, Cetirizine, Levocetrizine, Azelastine, Mizolastine, Ebastine and Rupatidine

Antihistaminics – Pharmacological actions

- Antagonism of Histamine:
  - Effectively block bronchoconstriction, contraction of intestinal and other smooth muscles and triple response
  - Low dose BP fall antagonized, but needs H_2 blockers to counter high dose fall in BP
  - Constriction of large vessels also antagonized
  - Gastric secretion – unchanged
- Antiallergic action: Manifestations of *Type 1* hypersensitivity reactions – suppressed
  - Urticaria, itching, angioedema – controlled
  - Anaphylactic fall in BP – partially prevented
  - Asthma in human – not affected (other mediators)

Antihistaminics – Pharmacological actions

- **CNS:** Variable degree of CNS depression (sedation)– depends on individual drugs – ability to cross BBB and CNS:Peripheral H1 receptor affinity
  - Inter-individual variation
  - Some Individuals: stimulant effects – restlessness and
  - Insomnia etc. 2nd generation – Non-sedating
  - Promethazine – controls motion sickness (unknown mechanism) and vomiting of pregnancy
  - Promethazine – controls rigidity and tremor in Parkinsonism
- **Anticholinergic:** Many are anticholinergic properties – Promethazine highest – additive action with Atropine, TCAs
- etc.
- **Local anaesthetic:** Pheniramine – membrane stabilizing effects –
- LA – but not used (Irritation) – also antiarrhytmic
- **BP:** Fall in BP with IV injection (all) but not with Oral

Pharmacokinetics

- Classically – lipid soluble, well absorbed orally and parenterally, metabolized in Liver and excreted in urine
  - Widely distributed in body and enters Brain and crosses BBB
  - Induce microsomal hepatic enzyme
  - Duration of action 4-6 Hours except …..
  - Cetirizine (C), loratadine (L), fexofenadine (F) - well absorbed and are excreted mainly unmetabolized form
  - C and L are primarily excreted in the urine
  - F is primarily excreted in the feces

ADRs - H_1- antgonists

- Frequent but mild – inter-individual difference to different drugs
  - Sedation (Paradoxical Excitation in children), diminished alertness, loss to concentrate, dizziness, motor incordination, tendency to fall asleep – commonest – say no to motor vehicle driving and operation
  - Alcohol synergises CNS effects
  - Tachydysrhythmias in overdose - rare
- Allergic reactions with topical use (contact dermatitis)
- Peripheral antimuscarinic effects
  - Dryness of mouth, blurred Vision, constipation, urinary retention
  - Epigastric distress and headache

- Acute overdose: CNS excitation, tremor hallucinations – resemble Atropine poisoning - death due to respiratory failure and CVS failure

Therapeutic uses

- Allergic reactions: Does not suppress AG:AB reaction – but blocks release of histamine – palliative
  - Itching, urticaria, seasonal hay fever, allergic conjunctivitis, angioedema of lips-eyelids etc. --- Laryngeal angioedema (Adrenaline)
  - Anaphylactic shock - cannot be relied
  - Less effective in perennial vasomotor rhinitis, atopic dermatitis, and chronic dermatitis – H_2 antagonist combination
  - Bronchial asthma – no use – 1) other mediators than histamine
    2) concentration at the site may not be sufficient
  - Not effective in humoral and cell mediated allergies
- Other conditions : (histamine) – Insect bite, Ivy poisoning –symptomatic relief
- Prunitides: Antipruritic - Independent of antihistaminic action
- Common cold: Symptomatic relief – older ones preferred

Antihistaminics - Therapeutic uses – contd.

- Motion Sickness: Promethazine, diphenhydramine, dimenhydrinate and cyclizine – 1 hour befor journey
  - Promethazine – morning sickness, drug induced and post operative vomiting and radiation vomiting
- Vertigo: Cinnarizine
- Preanaesthetic medication
- Cough: Chlorpheniraine maleate, diphenhydramine, promethazine etc.
- Parkinsonism: Promethazine – anticholinergic and sedative
- Acute muscular dystonia: Parenteral Promethazine – anti-dopamineric and antipsychotic drugs
- Sedative-hypnotic: Promethazine – respiratory depression (not below 2 years) – not preferred …… Hydroxyzine

2nd Generation antihistaminics

- **2nd generation (SGAs)** – after 1980s
  - Higher affinity for H_1 receptors: no anticholinergic side effects
  - Absence of CNS depressant property
  - Additional antiallergic – LT and PAF inhibition
- **Advantages over 1st generation:**
  - No psychomotor impairment – driving etc. can be allowed
  - No subjective effect
  - No sleep induction
  - Do not potentiate BDZ and alcohol etc.

Individual Antihistaminics

2nd Generation: in general, these agents have a much lower incidence of adverse effects than the first generation agents

- **Fexofenadine:** First non-sedating SGA- banned – Torades de pointes … when co-administered with CYP3A4 inhibitors – erythromycin, clarithromycin, ketoconazole and itraconazole etc.
  - Blocking of delayed rectifier K+ channel in Heart at high doses
  - Terfenadine, Astimazole etc. – banned
- **Loratidine:** Long acting, selective peripheral H1 blocker – fast acting and lacks CNS depression – metabolized by CYP3A4 (to an active metabolite)
  - No interaction with macrolides and no arrhythmias
  - Uses: Urticaria and atopic dermatitis
- **Desloratidine:** Metabolite of Loratidine – with its double potency

Individual Antihistaminics – contd.

- **Cetirizine:** Most commonly used these days (Levocetirizine – same with lesser side effects)
  - High affinity for Peripheral H1 receptor, but poor BBB cross, but somnolence at high dose
  - Not metabolized in body, no cardiac action when given with macrolides etc.
  - Other anti-allergic action – inhibits histamine and cytotoxic material release fro platelets and eosinophils
  - High skin concentration – beneficial urticaria and atopic dermatitis
  - Longer half life – once daily dosing
  - **Uses:** Upper respiratory allergies, pollinosis, urticaria and atopic dermatitis and seasonal asthma

Individual Antihistaminics – contd.

- **Azelastine:** H_1 blocker with topical action – also inhibitor of inflammatory response mediated by LT and PAF
  - Down regulation of Intracellular adhesion molecule-1 (ICAM-1) expression on nasal mucosa – Intranasal application
  - Half-life 24 hours but action lasts longer due to active metabolites
  - Used intranasal in seasonal and perennial rhinitis
- **Mizolastine:** Non-sedating – effective in rhinitis and urticaria (no active metabolite)
  - Half-life 8-10 Hours but single dosing
- **Ebastine:** Newer SGA – converts to carbastine
  - Half-life: 10-16 Hrs and non-sedating
  - Used in nasal and skin allergies
  - Arrhythmogenic potential

H_2-receptor antagonists

Cimetidine, Ranitidine, Famotidine and Roxatidine …..

….. Will be discussed later – in "Drugs for Peptic Ulcer"

What to remember?

- Histamine – Physiological Roles
- Histamine receptors – locations and actions
- Important antihistaminics – 1st generation and 2nd generation
- 1st generation Vs 2nd generation
- Uses of antihistaminics
- Individual drugs – Promethazine, Fexofenadie, Cetirizine, Azelastine and Ebastine

Thank you