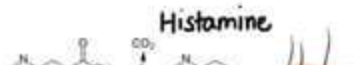
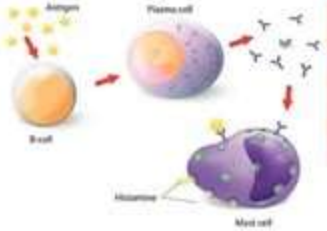
Histamine and anti histaminics

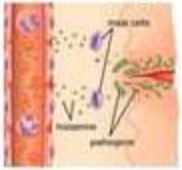
Histamine



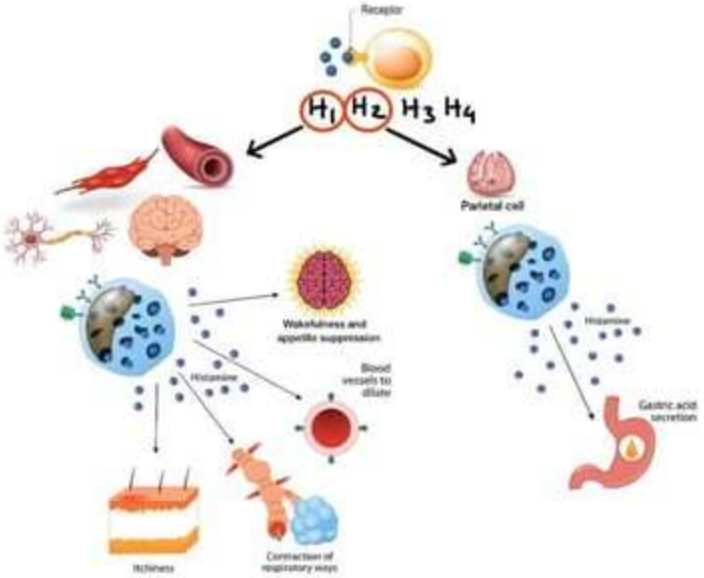
Allergic reaction



Tissue injury



Drugs & Foreign chemicals


Receptor
H1 H2 H3 H4
Parietal cell
Wakefulness and appetite suppression
Histamine
Blood vessels to dilate
Histamine
Gastric acid secretion
Itchiness
Contraction of respiratory ways

Introduction

- Histamine is an autocoid synthesised from amino acid histidine.
- Stored in granules of mast cells.
- Histamine acts on four receptors i.e H1 to H4.
- Well known mediator of allergic reactions like hives, allergic rhinitis,conjunctivitis, anaphylaxis.
- Regulate secretion of Hydrochloric Acid.

TYPE	LOCATION	FUNCTIONS
H1	Smooth muscles, endothelium, and CNS	• **Vasodilation**, • Bronchoconstriction • Separation of endothelial cells (responsible for hives), • **Pain and itching due to insect stings** • Primary receptors involved in allergic rhinitis symptoms and motion sickness • Sleep regulation
H2	Parietal cells	• **Primarily stimulate gastric acid secretion**

H3	CNS & to a lesser extent on PNS	• Decreased neurotransmitter release
		  • Histamine,
		  • Acetylcholine,
		  • Norepinephrine,
		  • Serotonin

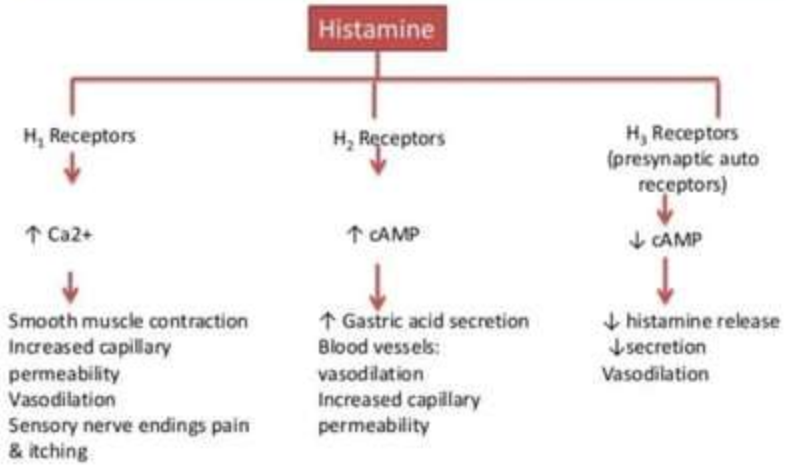
H4	Basophils & Bone marrow, Onthymus, Small intestine, Spleen, & colon.	• **Chemotaxis**.

- Histamine causes fall in blood pressure by acting on both H1 and H2 receptors.
- H1 stimulation causes vasodilation by releasing NO and H2 stimulation causes direct vasodilation.
- Pitolisant(Tiprolisant) acts on H3 receptors and helps in maintaining wakefulness.Approved for narcolepsy.
- Betahistine, a histamine analogue is used to control vertigo in Ménière's disease.

Drugs causing Histamine release

- D tubocurarine
- Morphine
- Atropine
- Polymyxin B
- Vancomycin

Mechanism of Action of Histamine



PHARMACOLOGICAL ACTIONS:

Blood vessels:

- **Histamine causes marked dilatation of smaller blood vessels, including arterioles, capillaries and venules.**

Heart:

- Primarily H2 responses but a H1 mediated negative dromotropic (slowing of A-V conduction)

Visceral smooth muscle:

- Bronchoconstriction;
- Abdominal cramps and colic by increasing intestinal contractions

Glands:

- Histamine causes marked increase in gastric secretion—primarily of acid but also of pepsin

Sensory nerve endings:

- Itching occurs when histamine is injected i.v. or intracutaneously.
- Higher concentrations injected more deeply cause pain.

Autonomic ganglia and adrenalmedulla:

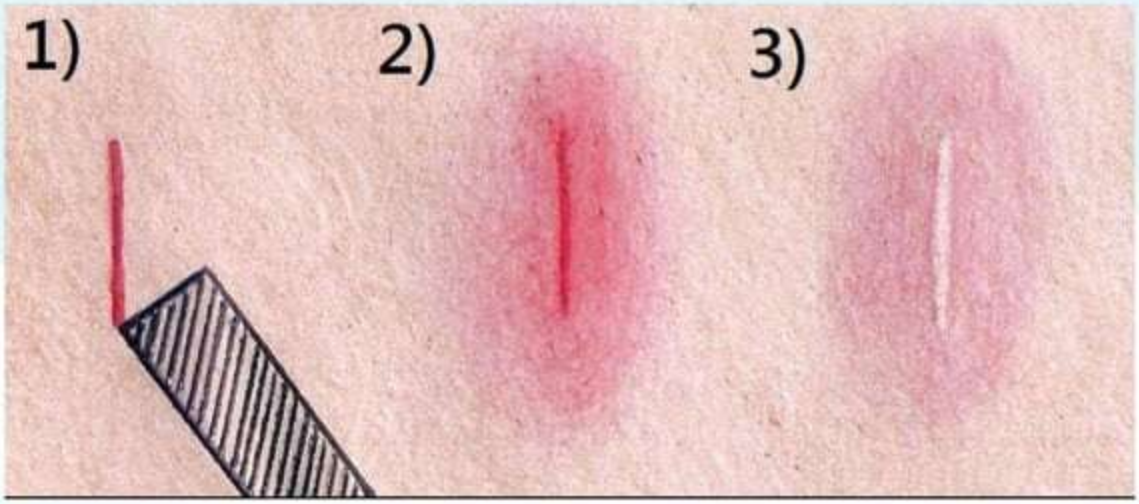
- These are stimulated and release of Adr occurs, which can cause a secondary rise in BP

CNS:

- Histamine does not penetrate bloodbrain barrier—no central effects are seen on i.v. injection.

GIT:

1. **Increase Gastric secretion**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2)
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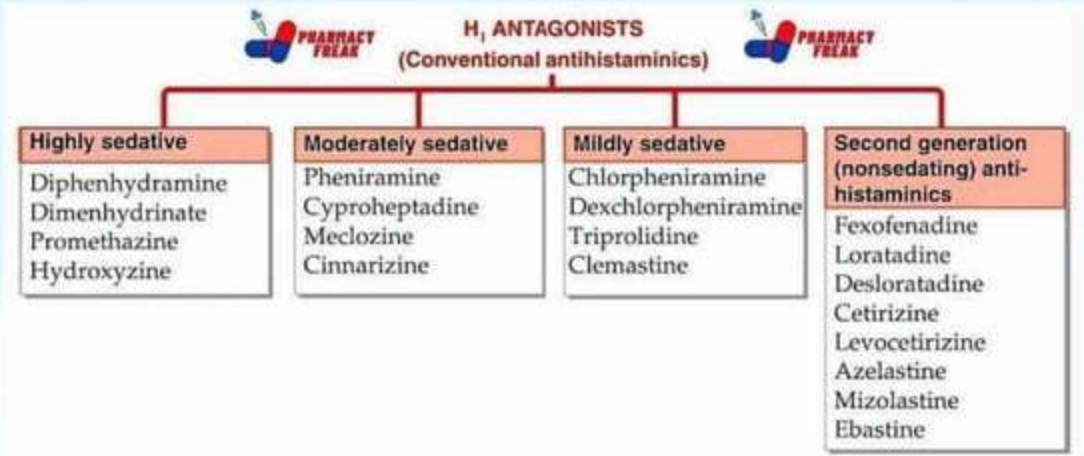
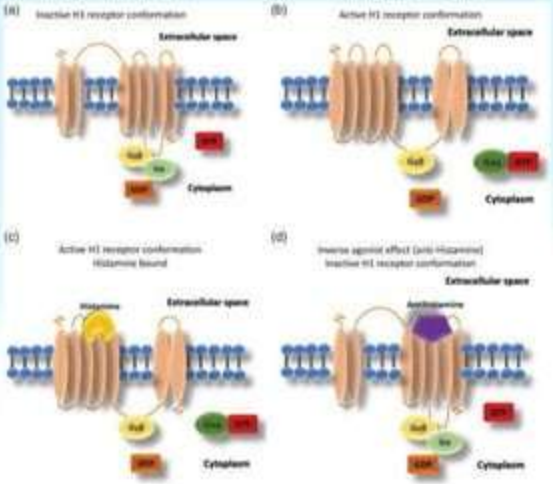

PHARMACY FREAK
H1 ANTAGONISTS
(Conventional antihistaminics)
PHARMACY FREAK
Highly sedative
Diphenhydramine
Dimenhydrinate
Promethazine
Hydroxyzine
Moderately sedative
Pheniramine
Cyproheptadine
Meclozine
Cinnarizine
Mildly sedative
Chlorpheniramine
Dexchlorpheniramine
Triprolidine
Clemastine
Second generation (nonsedating) anti-histaminics
Fexofenadine
Loratadine
Desloratadine
Cetirizine
Levocetirizine
Azelastine
Mizolastine
Ebastine

First vs second generation antihistaminics

- Blood brain barrier: first generation antihistaminics readily cross the blood brain barrier and cause sedation, cognitive and psychomotor impairment.
- Second generation have limitied penetration of BBB.
- Selectivity of H1 receptors:
- First generation antihistaminics have poor H1 selectivity and have additional anti muscarinic, anti adrenergic and anti serotonin activity.
- Second generation antihistaminics are highly selective for h1 receptors.

Mechanism of action of antihistamines

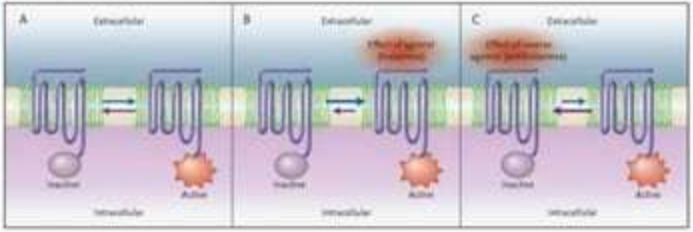
- H1 antihistamines are Inverse agonists
- They bund to inactive confirmation of H1 receptors and stabilise it.
- This produces pharmacological actions opposite to that of histamine.


(a)
Inactive H1 receptor conformation
Extracellular space
Cytoplasm
(b)
Active H1 receptor conformation
Extracellular space
Cytoplasm
(c)
Active H1 receptor conformation
Histamine bound
Histamine
Extracellular space
Cytoplasm
(d)
Inverse agonist effect (anti-Histamine)
Inactive H1 receptor conformation
Extracellular space
Cytoplasm

Antihistamines: Mechanism of action

Histamine receptors have basal activity which does not require the binding of an endogenous agonist histamine.

Histamine receptor blockers are **inverse agonists**. They stabilize the receptor in an inactive conformation making the excessive stimulation with histamine less possible.



Pharmacological actions of antihistamines

- Anti allergic actions:
- Counteract vasodilation, increased vascular permeability, sensitisation of nerve endings and bronchoconstriction induced by histamine.
- Allergic symptoms like erythema, edema, inflammation, sneezing, runny nose, red watery itchy ryes, urticaria are controlled.
- Anaphylactic fall in BP is partially prevented.
- Histamine induced bronchoconstriction is blocked.
- Antiallergic effect is shown by all H1 antihistaminics.

Effects on CNS

- First generation antihistaminics readily penetrate BBB and produce variable degree of CNS depression, sedation, cognitive and psychomotor impairment.
- Second generation antihistaminics have no cns depressant property and they are either non sedative or minimally sedative.

- Selectivity for H1 receptors:
- Second generation H1 receptors are highly selective.
- First generation H1 antihistaminics show varying degree of:
- Antimuscarinic action: Diphenhydramine
- Anti alpha adrenergic blockade: Promethazine
- Anti serotonergic action: cyproheptadine
- Local anesthetic action: diphenhydramine and promethazine

Adverse effects of first generation antihistaminics

- Rapidly cross BBB: produce cns depression, sedation, reduced cognitive and psychomotor performance.
- Antimuscarinic action: dryness of mouth, urinary retention and blurred vision
- Teratogenic effect: hydroxyzine, cyclizine and fexofenadine
- Block alpha adrenergic action: promethazine can cause hypotension, reflex tachycardia
- Acute overdosage: causes severe CNS and cardiac side effects. Can be fatal.

Uses of H1 Antihistaminics

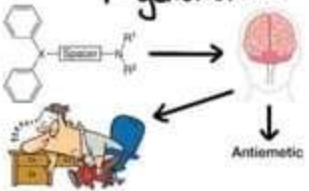
- Allergic disorders:
- Allergic conjunctivitis, allergic rhinitis, urticaria, dermographism, atopic eczema
- Acute allergic reactions to drugs, food et

Additional uses of first generation antihistaminics

- Sedatives: Promethazine, diphenhydramine
- Antiemetics: Promethazine, diphenhydramine, dimenhydrinate, doxylamine.
- Antiparkinsonism: Promethazine, cyproheptadine.
- Appetite stimulant: cyproheptadine.
- Anti tussive: Chlorphenoramine, Diphenhydramine, Promethazine.
- Local Anaesthetics: Pheniramine, Diphenhydramine

H1 Receptor Blockers
ANTIHISTAMINES

1st generation

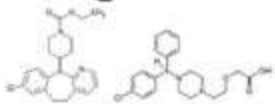


Brompheniramine
Chlorpheniramine
Clemastine

Cyproheptadine
Diphenhydramine
Doxylamine

Hydroxyzine
Meclizine
Promethazine

2nd generation



Cetirizine
Desloratadine
Fexofenadine

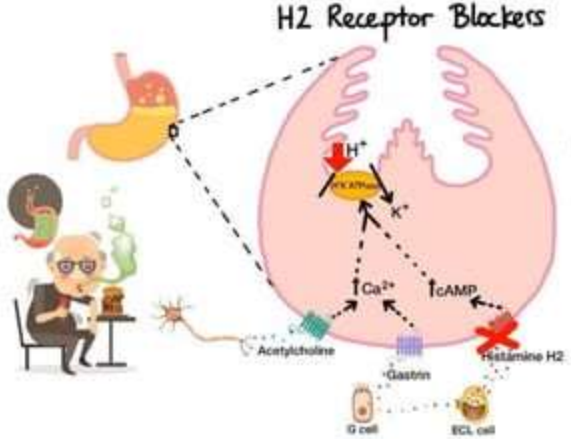
Levocetirizine
Loratadine

Azelastine
Olopatadine
Ketotifen

Pharmacology of H2 Antihistaminics

- Mechanism of Action: H2 antagonist
- Competitive: Cimetidine, Ranitidine and roxatidine.
- Non competitive: Famotidine
- Pharmacological action:
- Block H2 receptors on gastric parietal cells and inhibit secretion of Hydrochloric acid.
- Therapeutic uses: Peptic ulcers, GERD.

H2 Receptor Blockers



Cimetidine
Famotidine
Nizatidine
Ranitidine


Thank
you