Histamine and 5-HT

- Autacoid

autocrine effects

✓ Local effects → they are produced at site of need. eg, if in Liver, at liver itself

✓ Non-specific origin.

any cell can produce this.

⇒ This differentiates it from Hormones., cause, hormones are not produced locally, they are produced by specific cells only at carried to distantly located target organ.

Autacoids.

- amine → Histamine. 5-HT tryptamine.
- Lipid → PGs, LT
- peptide. → angiotensin, Bradykinin.

Histamine

H_1 ★ → main function → Allergy, wakefullness.

H_2

H_3

H_4.

① Allergy → through H_1

ie, anything that happens in allergy occurs through H_1

→ Vasodilation – H_1

→ Edema → Increase in vascular permeability → H_1.

→ Broncho constriction → H_1

② wakefullness – In Brain – H_1.

Histamine.

- H_1 → allergy, wakefulness
- H_2 → Stomach (↑HCl)
- H_3 → autoreceptor → Brain → presynaptic
- H_4 → WBC → Chemotaxis.

- H_2 blocker → used in peptic ulcer.
- H_3 blocker → Brain failure. → ↑ Histamine

Pitolisant (Tiprolisant) → used in condition where we need ↑ histamine. eg ↑ wakefullness ⇒ Narcolepsy

Narcolepsy

↓

pitolisant – H_3 blocker.

H_1 Blocker / H_1 Antihistaminic

↓

for ↓ allergy ★

H_1 blockers

- 1st Gen
  - BBB ✓ (cross).
  - sedation.
  - Non specific → also block M_1, M_2, M_3 → they have anticholinergic effect.
- 2nd Gen.
  - BBB ✗
  - less / No sedation
  - specific
    - only block H_1

- Why sedation ?

1st gen will cross BBB, and block H_1 receptor in Brain → but it's needed for wakefullness. ↓ if blocked → Sedation ★

H_3 blocker used in

↓

Narcolepsy

So, they'll ask questions like →

Truck driver had allergy, which antihistamine should not be given.

A) 2nd gen
B) 1st gen ✓
C) 2nd gen
D) 2nd gen

1st gen → X should not be given. → as it will cause sedation.

1st gen Antihistamines → also blocks Muscarinic receptor.
→ they are non-specific.
→ they have anti-cholinergic action.
→ they'll have side effects that anticholinergics have
ie, → dryness
blurring of vision
urinary retention
tachycardia
Mydriasis
1st → Can't be given ACG

But in some cases, we use them where we need anticholinergic property.

Uses

Parkinsonism – (drug induced)
Anti – acute muscular dystonia
cholinergic – common cold.
property – prophylaxis of motion sickness

Because of Anticholinergic action of 1st gen → apart from allergy, → they are also used in the above 4 situations

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parkinsonism – drug induced.
→ It occurs due to imbalance in dopamine & Ach.
→ drug causes ↓ dopamine.
→ we give anticholinergic so Ach activity also ↓
→ restor Ach : dopamine ratio.
→ Drug of choice in drug induced Parkinsonism → Benzhexol

• acute muscular dyst
is a similar condition
where we need to ↓ Ach
→ also use → Benzhexol

Common Cold – Viral.
→ runny nose.
2nd gen → eg cinnarizine can only treat runny nose due to allergy
→ Here, it's viral.
→ we use 1st gen that also has anti Ach action
→ ↑ dryness
→ treats Common Cold due to virus

2nd gen → Only used in Allergy

- TERFENADINE
- ASTEMIZOLE
- LORATIDINE
- CETIRIZINE
- AZELASTINE
- OLOP
- ~~FEXOFENADINE~~
- ~~DES-loratidine~~
- ~~Levo-cetirizine~~
- OLOPATADINE

XBBB
XAch

1st Generation Antihistamines

- promethazine
- Diphenhydramine.
- Dimenhydrinate.
- Pheniramine.
- Chorpheniramine
- cyclizine.
- Buclizine.
- Cinnarizine.

market name →
- PHENARGAN → max - BBB ✓ Antiholinergic.
- AVIL

BBB cross ✓
Antiholinergic ✓
allerg ✓

→ Best alternative of Benzhexol → promethazine.

Drugs ↑ QT Interval.

- Cisapride. — Banned.
- Astemizole — V. Imp.
- Terfenadine

CAT - Cute QT

- Terfenadine → Fexofenadine (metabolite) — XQT prolongation
- Astemizole

when overdosed →
Blocks K^+ channels.
↓
↑ QT interval.
↓
Torsades de pointes

Why overdosed?
they are metabolized by
CYP3A4 → microsomal enzyme (Inducers, Inhibition)
↓
Inhibited by → ciprofloxacin, erythromycin (antibiotics)

- Azelastine
- olopatadine

max Topical activity.

↓
- allergic conjuctivitis - eyedrops
- nasal spray etc..

3rd Gen Antihistamines

- they are actually metabolites of 1st gen.
- terfenadine → fexofenadine. ✓
- Des - loratidine → loratidine ✓
- levo - cetirizine → cetirizine.

5-HT

4 receptors → $5HT_1$, $5HT_2$, $5HT_3$, $5HT_4$

(T 5,6,7 are also there, but unknown locations & function)

$5HT_1$ → 1A, 1B/1D.

$5HT_{2A}$ / 2C.

5 Total.

- $5HT_{1A}$
- $5HT_{1B}$ / $5HT_{1D}$.
- $5HT_{2A}$ / $5HT_{2C}$.
- $5HT_3$
- $5HT_4$.

$5HT_{1A}$

(A) → autoreceptors.
- presynaptic.
- Break function
↓
↓ serotonin

- when serotonin ↑ → anxiety.
- so to reduce anxiety
→ $5HT_{1A}$ agonist is given
↓
Buspirone.

• Sab A hain?

→ A ka Against Anxiety

main dete hain kyonki

A - Adrenoreceptor hain.

---

when we give $5HT_{1A}$ agonist

of enhance brain

↓

Serotonin ↓

↓

Anxiety ↓

Anxiety medication

→ $5HT_{1A}$ agonist

↓

Buspirone

don't confuse with

Bupropione → anti smoking

Buspirone → anxiety

$5HT_{1B}$ / $5HT_{1D}$

B - blood vessel → Brain's blood vessel

D - dimare → brain

they cause

↓

Vasoconstriction

↓

of Blood vessels in

↓

Brain.

✓ when is VC in brain vessels required

↓

During headaches

↓

Cause vasodilation occurs in headaches

↓

used to treat migraine.

ERGOTAMINE.

Triptan

Sumatriptan

Naratriptan.

Eletriptan.

Zolmitriptan.

Rizatriptane.

↓

DOC of acute migraine.

↓

they activate $5HT_{1B}$ / $5HT_{1D}$ receptors.

$5HT_{2A/2C}$ Blockers

↓

antipsychotic drugs

typical → D_2 blocker

atypical → $5HT_{2A/2C}$ blockers

• Clozapine

side effect → weight gain.

• If we stimulate 5HT receptors

↓

will it cause weight loss

↓

Yes!

↓

LORCASERIN

↓

approved drug in obesity

↓

It is $5HT_{2A/2C}$ stimulant/agonist.

$5HT_3$.

• CTZ - Isotropic receptor

• all serotonic receptors are GPCRs

↓

Except

↓

$5HT_3$ → Ionotropic

↓

CT2.

---

when CT2 is stimulated

↓

vomiting.

→ Anticancer drugs

↓

Induces vomiting.

↓

due to 5HT3 stimulation

↓

CINV

Chemotherapy Induced Nausea Vomiting.

So if we block 5HT3.

↓

Nausea & vomiting won't occur during Chemotherapy

↓

Setrons – 5HT3 blocker

ONDAN setron.
GRANI setron.
Tropi setron.
Palano setron.
Dola setron.

CINV

early (<24hr) → setrons ✓ (99%) early

delayed (>24hr onset) → setrons X → aprepitant (rare)

setrons only work in early CINV ✓

not in delayed CINV.

*In delayed (rare)

↓

aprepitant.

5HT3 blockers – setrons are DOC in (3).

CINV | radio therapy | post op.

Nausea, vomiting.

ONDAN setron.

↓

additional use:

↓

can reduce.

Alcohol craving.

5HT4

- located in upper GIT.
- they ↑ motility (stimulated) → of upper GIT.

↑ motility : PROKINETIC

Cisapride
Mosapride
Prucalopride
Tegaserod.

5HT4 agonist.

Domperidone.

(5HT4 agonist PROKINETIC) are used in

↓

✗ constipation (lower git)

✓ GERD

↓

Stomach acids reach Oesophagus by travelling up.

↓

So ↑ Oesophagus, we can get it back to stomach by ↑ forward movement

↓

✓ prokinetics

- In GERD.

↓

we can also use proton pump inhibitors

↓

HCl secretion inhibit.

↓

Proton pump inhibitors

↓

prazole – Omiprazole.

DOC in GERD.

↓

PPI – Omiprazole. pantoprazole.

↓

In clinical practice, we use both.

eg: Pan D

pantoprazole | Domperidone (prokinetic)

Due.

QT prolongation

↓

Cisapride is Banned

C – Cisapride.
A – Azelanezole
T – Terfenadine.

↓

QT prolongation

✗ Banned

Histamine - Sair.

Histamine → β-imidazolethylamine

Histamine synthesis & metabolism

Histidine
↓ Histidine decarboxylase.
Histamine
- Diamine oxidase → Imidazole acetic acid.
- N-methyl Transferase → N-methyl histamine
  ↓ MAO.
  N methyl imidazole acetic acid.

Storage

- In granules in mast cells.
- histamine (+) → held by (-) proteins & heparin.
  ↓
  released → Na+ in ECF exchange with Histamine.
  ↓
  Histamine readily released when needed.

Distribution.

- Skin, Intestine, Lung, placenta, liver.
- Non mast cell histamine
  ↓
  Brain, epidermis, gastric mucosa & growing regions.
  (fast turnover)
  ↓ enterochromaffin (cell)

↑ cAMP (-) histamine.
- Ineffective orally
  ↓
  Liver degradation.

Histamine receptors.

H_1, H_2, H_3 - autorec..., H_4

- all are GPCR's

LOCATION

H_1 → Smooth muscle → Intestine, airway, uterus → Contraction

Blood vessels → Endothelium
↓ Small.
release of NO, PGI_2
↓
- vasodilation
- ↑ vascular permeability

Smooth muscle of larger vessels
- vasoconstriction.

- Afferent nerve endings – stimulation
- Ganglionic cell – stimulation
- Adrenal medulla – CA release.
- Brain – Impulse.

H_2 →
- Gastric glands – acid secretion
- Blood vessel (smooth muscle) → dilation
- Heart → atria, ventricle → + inotropy
- Uterus – relaxation.
- Brain (postsynaptic) Impulse.

H_1 → Smooth muscle → Vasoconstriction
H_2 → Smooth muscle → Vasodilation

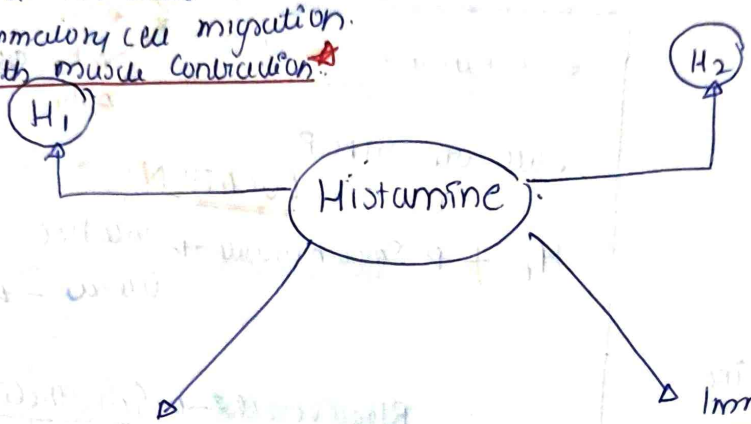
Allergic reaction

- Vasodilation → small vessels.
- ↑ Capillary permeability → Extravasation → edema.
- adhesion molecules → Inflammatory cell migration.
- Smooth muscle contraction ★

Gastric acid secretion

↑ Gastric acid secretion.

- Smooth muscle relaxation ★
- Cardiac Stimulation.



Neurotransmission

- wakefulness, cognition.

Immune Inflammation

- Immune cell chemotaxis
- cytokine secretion
- Immune inflammation.

Pharmacological Action

(1) Blood vessels

- Histamine → marked vasodilation of smaller blood vessels. ★

- S.C → (small dose)
  - flushing, heat etc.. vasodilation
  - but little to no fall in BP ★
  - due to ↑ HR & C.O by Compensatory Sympathetic system activation.

- Rapid IV → (large dose)
  - short lasting H_1 slow but more persistant H_2 component
  - Vasodilation of large vessels
  - marked fall in BP → prevented by H_1 & H_2 blocker

- small dose → only H_1 manifest
- large dose → H_2 is predominant

But only in blood vessels, not in GIT, organs etc..

there → always H_1 predominant irrespective of dose.

Intradermal injection → triple response → red spot : due to intense capillary dilatation
wheal : due to fluid exudation
Flare : redness due to dilatation of arterioles.

2. Heart

- H_2 receptor
- rate ↑, FOC ↑

3. Visceral Smooth Muscle

H_1 action predominant
- Bronchoconstriction
- Large dose → abdominal cramps / colic → due to ↑ intestinal contraction ✓

no much effect on other smooth muscle

4. Glands

↑ in gastric secretion.
- H_2 receptor on parietal cell (+)
- ↑ cAMP
- (+) membrane proton pump (H^+-K^+ ATPase)

5. Sensory / Afferent Nerve Ending - Stimulation.

- stimulation of sensory nerve endings → pain, itching
- IV, S.C → Itching.
- high dose → pain dup.

6. Autonomic Ganglia

(+)

7. Adrenal medulla

Adrenaline (catecholamines) is released.
↓
Secondary rise in BP

7. CNS

- Histamine – BBB ✗ not crossed
- IV → no cerebral effects.

PATHOPHYSIOLOGICAL ROLES

① gastric acid secretion

② allergic phenomenon → Histamine
- is responsible for → Urticaria, angio edema, Bronchoconstriction, anaphylactic shock ✗
- only in immediate reactions ✓

treatment
↓
H_1 antagonist
except asthma, anaphylactic shock.
↓ in BP

LTD4, PAF

① Second generation Anti-histaminic

properties

* No CNS depressant properties – doesn't cross BBB
* More H_1 selectivity: no anticholinergic side effects.
* addition anti allergic mechanism apart from histamine blockade.

Advantages

* doesn't impair psychomotor performance.
* Produce no subjective effects
* No sedation.
* Does not potentiate alcohol or benzodiazepines.

DISADvantages

itch relief.

- poor anti-pruritic, anti-emetic, anti-tussive actions.
  cough relief

Limitations

- have narrow spectrum of therapeutic usefulness because it depends on the extent of involvement of H_1 receptors.
  (not effective in asthma)

DRUGS

- Loratidine
- Rupatadine.
- Cetirizine.
- Azelastine
- Mizolastine.
- Ebastine
-

- metabc

Second Generation Antihistaminics.

properties

- donot have CNS depressant properties.
- have more H_1 sensitivity: no anticholinergic side effects.
- Additional Anti-allergic properties apart from H_1 receptor blockade.

Advantages

- do not impair psychomotor performance.
- No subjective effects.
- No sleepiness.
- does not potentiate alcohol & benzodiazepines.
- No anticholinergic side effects.

Disadvantages → poor antipruritic, anticonvulsant & antitussive action

Limitation narrow therapeutic usefulness as they work by blocking H_1 receptors only. spectrum of.

Drugs → Cetirizine ☆
Loratadine ☆
Azelastine ☆
Mizolastine.
ebastine
Rupatadine.

Uses → allergic disorders
cough
pruritides.
Motion sickness
vertigo.
symptomatic relief in Insect bite & Wy poisoning.
- drug induced parkinsonism.

Cetirizine:

- metabolite of hydroxyzine with marked affinity to peripheral H_1 receptors.
- poor CNS penetration.
- but mild sedation - some.
- Inhibit histamine & cytotoxic mediator release from platelets
- Inhibit chemotaxis of eosinophils.
- Superior efficacy in urticaria & Atopic dermatitis → attains higher & longer lasting conc. in skin.

Elimination T1/2 - 7 - 10 h.
Indications: atopic d, urticaria, URT allergy. pollinosis
ADR → Mild sedation. adjuvant in seasonal asthma.
light headedness.
Acute overdose - central excitation, hallucinations, tremor

- Cetirizine is not metabolized.
- does not prolong cardiac action potential / produce arrhythmias when given with Ketoconazole / erythromycin.

X ——————— X

Loratidine

- selective.
- long acting peripheral H_1 antagonist.
- No CNS depression.
- metabolized by CYP3A4

↓

active metabolite

longer T½ – 17 hours.

Uses: Urticaria & atopic dermatitis

Azelastine.

- good topical activity
- addition to H_1 blockade – (-) histamine release and inflammatory reaction triggered by LTs & PAF.
- down regulates ICAM-1
- metabolized by CYP34A.

Mizolastine

- Non sedating antihistaminic
- T½ – 8 – 10 hours.

Ebastine

- pro drug.
- active form – Carebastine.
- T½ – 15 – 19 h.

Rupatidine.

- additional PAF antagonistic property