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Antihistamines

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Histamine

- autacoid (local hormone)
- endogenous amine (hydrophilic)
- in tissues is formed from histidine

Location: in granules in mast cells, basophiles (histaminocytes) → bound to heparan sulphate and acidic protein

in almost all tissues, highest levels in lungs, GIT, skin

Main roles in the body:

neurotransmitter – **CNS**

mediator of allergic/inflammatory reactions – **mast cells, basophilles**

regulation of gastric acid release (↑) - **stomach**

Histamine

is released from mast cells granules by exocytosis
(activation of phospholipase C a ↑ Ca^{2+})

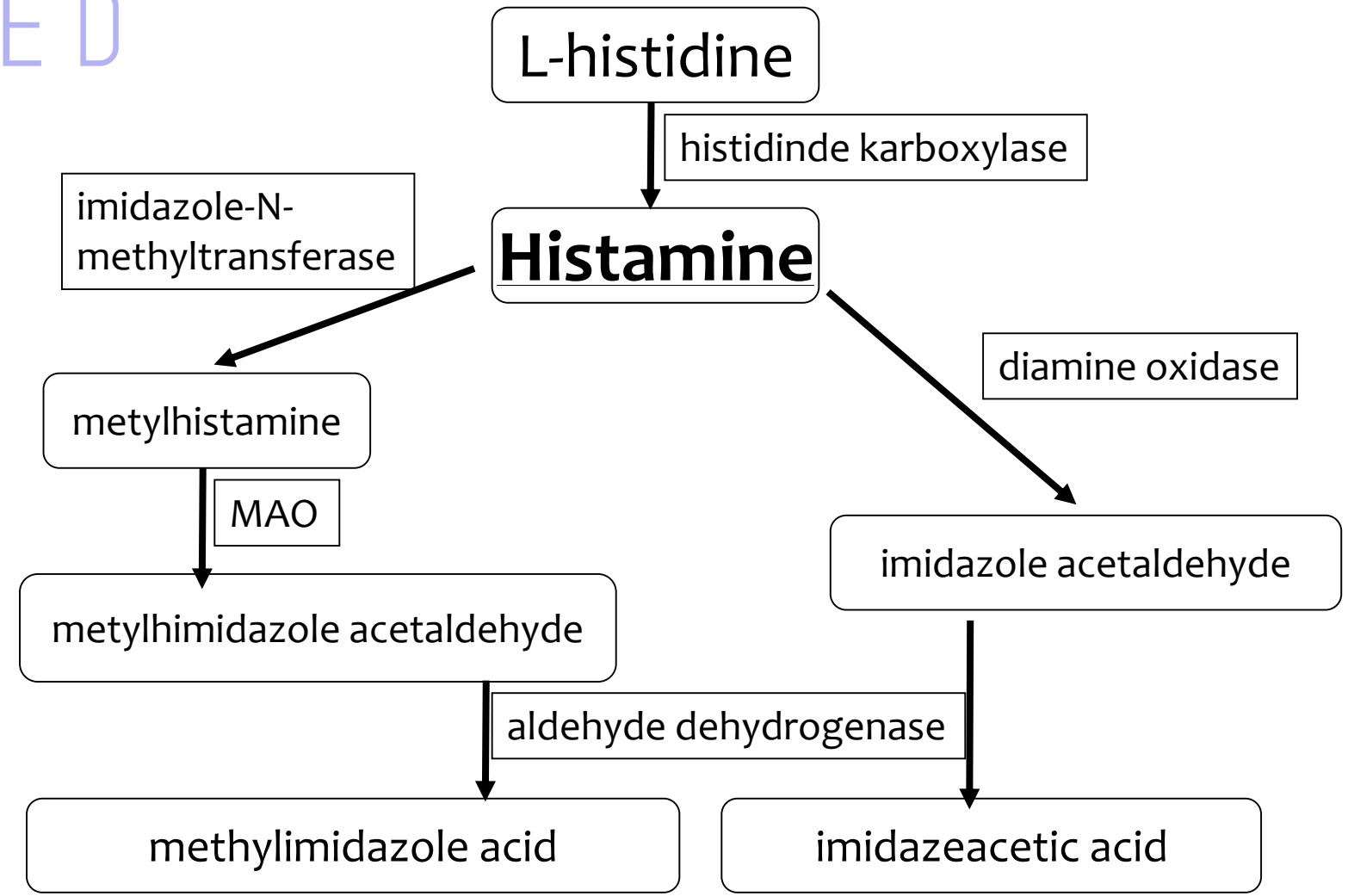
Stimuli:

imunological: antigen + IgE

physical, chemical or mechanical cell damage

drugs

Histamine metabolism



Histamine receptors

4 subtypes (H_1 – H_4)

G protein-coupled receptors

their stimulation results in increase in cellular concentration of Ca^{2+} ions

H_1 receptors

postsynaptic, G_q-protein ↑ phospholipase C →
↑ IP3 and DAG → ↑ Ca^{2+}

Location:

endothel, smooth muscles (vessels, bronchi, uterus, GIT), peripheral neuron ending, CNS

Effects:

smooth muscle contraction (bronchi, uterus, ileum)

vasodilatation of minor vessels (↓BP, reddening of skin)

increase in vessel permeability (swelling)

irritation of peripheral neuron endings (itching, even pain)

excitation of CNS

H_2 receptors

postsynaptic, G_s-protein ↑ activity of adenylate cyclase → ↑cAMP

Location:

stomach mucosa, heart, vessels, immune system

Effect:

in stomach: gastric acid, pepsine, intrinsic factor secretion

slower and longer vasodilatation

+ inotropic, + chronotropic effect

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H_3 receptors

presynaptic, G_i protein → inhibition of N-type Ca^{2+} channels
→ ↓ cellular Ca^{2+}
feedback inhibition of histamine release

heteroreceptors, ↓ release of other neurotransmitters

Location:

mainly in CNS (but in PNS tissues as well)

Effects:

sedation
negative chronotropic effect
bronchoconstriction

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H_4 receptors

possibly isoform of H_3

Location:

eosinophiles, basophiles, bone marrow, thymus, intestine, spleen

Effects:

influencing activity of immune system
important for chemotaxis

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How to antagonize effects of histamine?

Treat the symptom

vasoconstrictiors, sedatives, antacides, tocolytics etc.

Treat the cause

inhibition of synthesis (glucocorticoids)

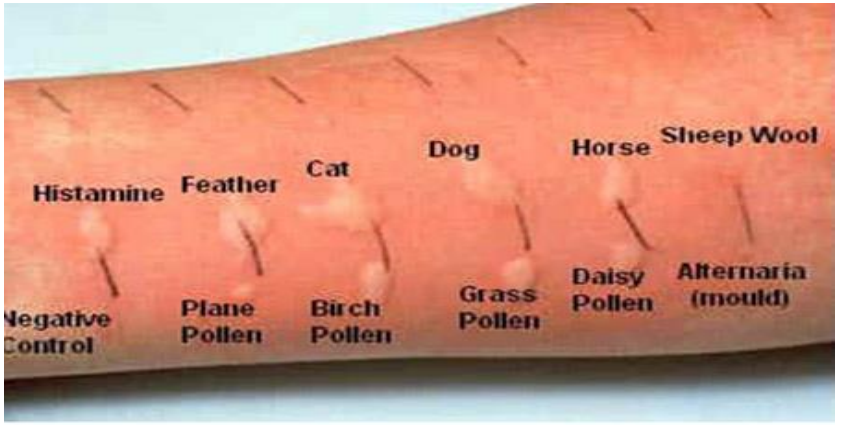
inhibition of release (cromoglycate, nedokromil, β_2-SM, glucocorticoids)

receptor antagonism:

- non-specifically, indirectly (epinephrine)
- specifically, directly (H1, H2, H3 - antihistaminines)

Histamine in clinical practise

limited use (ineffective when given orally)
diagnostics in allergology



Skin Allergy Test

histamine analogue → **betahistine**

Lewis reaction

typical response to intradermal histamine administration:

skin reddening (vasodilatation of arterioles)

wheal (capillary permeability)

flare (redness in the surrounding area due to arteriolar dilatation mediated by axon reflex)

used in allergy testing – positive control

it is used to evaluate the potential antiallergic effect of H1 antihistamines

Allergy

has a high incidence, 10-30% (and growing)

genetic factors

various theories about its origin

<u>Mechanism of alergic reaction:</u>

early contact with allergen

allergen binds to IgE antibody

degranulation of cells containing histamine

activation of phospholipase C

→ mobilization of intracellular Ca^{2+}

→ mediators are released: HIS, PG, LT, PAF, cytokines

Allergy treatment

always as an addition to taking enviromental control measures and avoiding allergen

H_1- antihistamines

glucocorticoids

mast cells stabilizers

immunotherapy

epinephrine (anaphylactic shock)

H_1 antihistamines

MoA: antagonization of H_1 receptor

they antagonize the allergy symptomes caused by histamine

high selectivity to H_1 rp. → low affinity to H_2 rp.

3 generations

AE:

antimuskaric, antiserotonergic a antiadrenergic effects of older drugs of this group (sedation, fluctuating blood presure,...)

block of Na^+ channels → locally anaesthetic and antipruritic effect

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H_1 antihistamines pharmacokinetics

Dosage forms:
oral, topical, parenteral (i.m., infusion)

easy and quickly absorbed from GIT

distributed evenly in the body

metabolized in liver (some in form of prodrug)

excreted in urine, stool

drugs of I. generation cross the blood-brain barrier → central effects (sedation)

cross the placenta and are distributed into milk!

H_1 antihistamines - I. generation

relatively old drugs

in general lower selectivity to H_1 receptors

they cross the **blood-brain barrier**

effect lasts **approx. 4 - 6 h**

rather common adverse effects

dimetinden (Fenistil®)

promethazine

bisulepin (Dithiaden®)

moxastine – for motion sickness (Kinedryl®)

cyproheptadine – treatment of serotonin syndrome

ketotifen

H_1 antihistamines
AE of I. generation

sedative, even hypnotic eff.– driving, heavy mashinery operation (!)

paradoxical reaction (children, elderly) = excitation (sleeplessness, nervousness, tachycardia, tremor, ...)

indigestion (nausea, vomiting, diarrhea x constipation)

skin symptoms → phototoxicity

anticholinergic effects

increas in appetite (antiserotoninergic effect)

ortostatic hypotension (weak block of α-adrenergic rp.)

H_1 antihistamines
II. and III. generation

- low distribution to CNS – minimal sedative effect

- better properties – higher selectivity towards rp., less AE

- effect lasts for **12 – 24 hours,** given 1 - 2 times a day

II. generation

- cetirizine
- loratadine
- fexofenadine
- azelastine
- levocabastine

III. generation

- levocetirizine
- desloratadine
- bilastine
- rupatadine

Novel H_1 antihistamines III. generation

bilastine

high selectivity towards H_1-receptors, antiinflammatory properties

not metabolized by liver or intestinal wall, low potential for drug-drug interaction

rupatadine

long-term effect

dual effect (H_1 antagonist + blocks PAF receptors)

H_1 antihistamines
AE of II. generation

arrythmogenic→ QT interval prolongation (some drugs even withdrawn)

possible sedation when overdosed (cetirizine)

Interactions:

are metabolised by CYP3A4 → be cautious of inhibitors of this isoform (macrolide ATB, azole antifungals, verapamil, grapefruit juice...)

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H_1 antihistamines Indications I

treatment of symptoms of **allergic diseases**
- allergic rhinitis
- urticaria, drug and food allergy

add-on treatment of anafylactic reactions

pruritus of various ethiology (e.g. itching in allergic and non-allergic dermatitis + insect bites)

tinitus, Meniére's disease

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H_1 antihistamines Indications II

migraine

nausea a vomiting
movement sickness (moxastine, embramine)
vertigo

prophylactic premedication before some drugs (e.g. monoclonal antibodies)

sleeplessness, when hypnotics are not tolerated

anxiety (hydroxyzine → mild anxiolytic effect)

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H_1 antihistamines Contraindications

- alcohol dependency
- hypersensitiveness to that substance
- serious hypotension
- simultaneous administration of sedative drugs (I.generation)
- activities which require full attention (I.generation)
- patients with history of arrythmias (II. generation)

H_3 antihistamines

betahistine

MoA: H_3 antagonist, H_1 agonist
analogue of histamine

improves microcirculation of the inner ear by vasodilatating capillaries

indications: tinitus, vertigo, Menière‘s disease