Antihistamines

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

Histamin 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 (!!!)

Effect:

- 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

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)

Effect:

- sedation
- negative chronotropic effect
- bronchoconstriction

H_4 receptors

- possibly isoform of H_3

Location:

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

Effect:

  - influencing activity of immune system
  - important for chemotaxis

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 alergology
- histamine analogue → **betahistin**

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
- is used to evaluate the potential antialergic effect of H1 antihistamines

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 antihistaminines

- **MoA: reversible competitive antagonism**
- they antagonize the allergy symptomes caused by histamine
- high selectivity to H_1 rp. → low affinity to H_2 rp.
- 3 generations

- **AE:**
  - **antimuscaric, antiserotonergic a antiadrenergic** effects of older drugs of this group (sedation, fluctuating blood presure,...)
  - **block of Na^+ channels** → locally anaesthetic and antipruritic effect

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**
- **promethazine**
- **bisulepin**
- **moxastine** – for motion sickness
- **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 (nauzea, vomiting, diarrhoea x constipation)
- skin symptoms → phototoxicity
- anticholinergic effects
- increasment in appetite (antiserotoninergic effect)
- **ortostatic hypotension** (weak block of α-adrenergic rp.)

H_1 antihistamines
II. a III. generation

- low distribution to CNS – minimal sedative effect
- better properties – higher selectivity towards rp., less adverse effects
- effect lasts for **12 – 24 hours,** given 1 - 2 times a day

II. generation

- cetirizine
- loratadine
- fexofenadine

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

H_1 antihistamines
Indication

- 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**
- **migraine**
- **nausea a vomiting**
  - movement sickness (moxastine, embramine)
  - vertigo
- **prophylactic premedication** before some drugs (e.g. monoclonal antibodies) – I. generation
- **sleeplessness**, when hypnotics are not tolerated
- **anxiety** (hydroxyzine → mild anxiolytic effect)

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