H_1 ANTIHISTAMINES

Histamine, histamin receptors, H_1 antihistamines

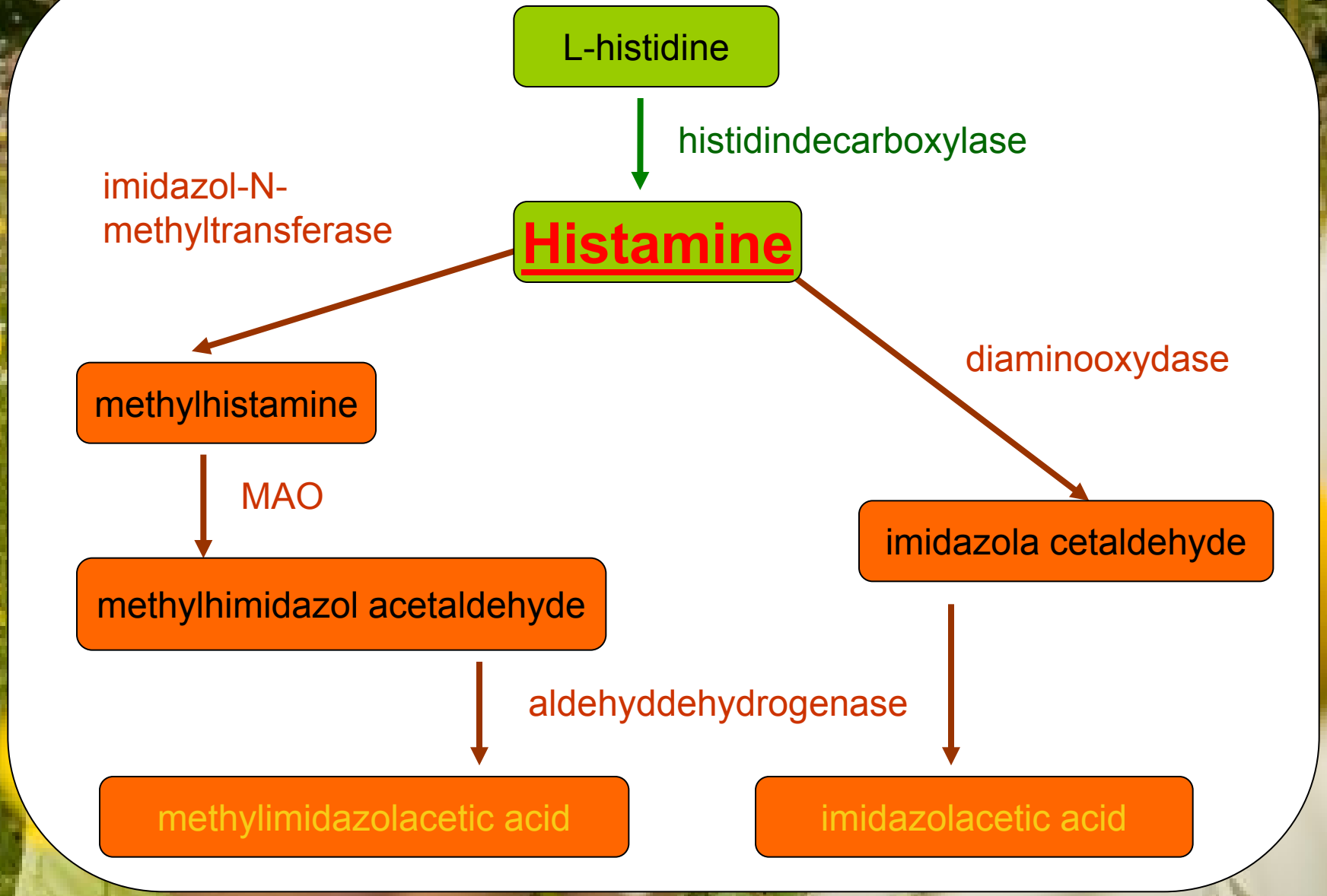
PharmDr. Ondřej Zendulka, Ph.D.

HISTAMINE

- biogenic amine, autacoid
- in plants and animals as well
- human – 3 functions
    - allergy mediator
    - HCl prosuction
    - neurotransmitter

- stored in mast cells
- impulses for histamin release:
    1. antigen + IgE
    2. physical influence
    3. drugs

HISTAMIN- metabolismus



HISTAMINE - receptors

- subtypes H_1-H_4
- G protein coupled
- stimulation = changes in intracelullar Ca^{2+} concentration

H_1

- endotel, smooth muscles of GIT, uterus and bronchi
- capillary permeability increase, smooth muscles contractions, nervous system – CNS allertnes, PNS sensitive neurons stimulation

H_2

- gastric mucosa, imune system, vessels
- HCl secretion, + ino a chronotropic effect - vasodilation

HISTAMINE - receptors

H_3

- CNS and PNS
- negative feedback of histamine liberation
- sedation, negative chronotropic action, bronchoconstriction

H_4

- basophils, bone marrow, thymus, intestine, spleen
- infleance on immune system activity
- essential for chemotaxis

HISTAMINE - effects

CVS

- vazodilation - H_1 a H_2 receptors
- ↓ BP, ↑ capillary permeability
- + chronotroic and inotropic effect H_2 Rc

Neurons

- itching, pain H_1 Rc

CNS

- regulation of vigilance

GIT

- HCl secretion H_2 Rc
- smooth muscle contraction H_1 Rc

HISTAMINE - effects

Erection

- H_2 receptors

Uterus

- contraction

Skin

- Lewis reaction (triple response)
    - capillary smooth muscle – red colour
    - capillary endothelium - swelling
    - sensory nerves –itching/pain

HISTAMINE - effects

Antagonism of histamine effects

Symptomatic

- **vasoconstring. agents, sedatives, antacids, tocolytics atc.**

Causal

- **synthesis inhibition - glucocorticoids**
- **release inhibition– cromoglycate, nedocromil, betablockers, glucocorticoids**
- **receptor blockade**
  - **indirect – epinephrine**
  - **selective H_1 H_2 antihistamines**

Antihistamines - allergy

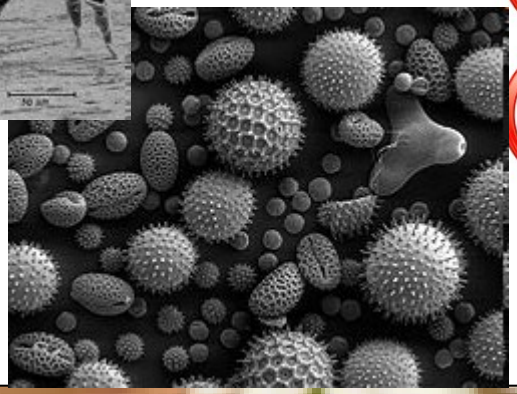
Alergie

- inappropriate immune system reaction to harmless environmental substances
- frequent illness 10-30%
- increasing incidence
- hereditary

Antihistamines - allergy

Allergens

- nonparasitic antigens causes I. type of hypersensitivity
- herbal, animal, synthetic



Antihistamines - allergy

Allergic reaction

- acute response – reaction on antigen, histamine release, production of IL 4 and IgE

- late-phase response – with 4 and more hours of onset

  - migration of leukocytes into site of reaction and development of inflammation

Antihistamines - allergy

Allergic reaction symptoms

- allergic rinitis
- allergic conjunctivitis
- allergic skin reaction
- allergic eczema
- allergic asthma
- anaphylactic reakce

Antihistamines - allergy

Diagnostic tools

- case history
- intradermal or prick tests
  - set of allergens is tested
  - principle – local allergic reaction is evoked

- http://www.youtube.com/watch?v=5i5ni8E0spc
- http://www.youtube.com/watch?v=4-tyrYDgTQw&feature=related
- http://www.youtube.com/watch?v=CvUp6eqdG88&feature=related

Lewis reaction

- after histamine intradermal injection

Antihistamines - allergy

Therapy

- prevention
- Immunotherapy
  - hyposensitisation + sublingual immunotherapy (SIT)
  - Omalizumab – anti IgE
- Pharmacotherapy
  - epinephrine – anaphylactic reaction
  - corticoids
  - H_1 antihistamines

H_1 Antihistamines

- H_1 receptors competetive antagonists
- high specificity against H_1 subtype
- II. gen. – irreversible bound to Rc
- all administration routes
- classification into 2 generations

Indications: pharmacotherapy of allergic reactions
adjuvans in therapy of anaphylaxis
pruritus
insect bite or sting
nausea, vomitus
insomnia
loc. anaesthesia

H_1 Antihistamines

Effects

- smooth muscles – block of bronchoconstriction and decrease of GIT smooth muscle tone

- vessels - vasodilation block (partially via – H_2 Rc)
  - ↓ capillary permeability

- nervous system - CNS inhibition - sedation
  - local anaesthetic effect
  - block of sensitive nerves irritation

H_1 Antihistamines

I. generation

- less selective to H_1
- cross BBB
- action lasts for 4-6h
- higher incidence of side effects

AE: sedation
antimuscarinic (atropine) activity
allergy
paradox stimulation
abdominal dyscomfort
antiserotonine and antiadrenergic effect

H_1 Antihistamines

I. generation

- clemastine (Tavegyl)
- dimetindene (Fenistil, Vibrocil)
- promethazine (Coldrex, Prothazin)
- bisulepine (Dithiaden)
- cyproheptadine (Peritol)
- antazoline (Spersallerg, Sanorin-Analergin)
- diphenhydramine (Psilo-Balsam)
- ketotifene (Zaditen, Ketotifen)
- chlorphenamine (Grippostad, Humex, Trigrip)
- azelastine (Alergodil)

- embramine (Medrin)
- moxastine (Kinedryl)

H_1 Antihistamines

II. generation

- higher selectivity against H_1
- do not cross BBB = sedative activity not present
- lower incidence of adverse effects
- long biol. halftime 12-24h

Adverse effects:

arythmias (terfenadinue and astemizole)
sedation after overdosing
inhibition of P450

H_1 Antihistamines

II. generation

- cetirizine (Analergin, Zyrtec, Zodac)
- levocetirizine (Sintir, Xyzal)
- loratadine (Claritine, Flonidan, Roletra)
- desloratadine (Aerius, Azomyr, Neoclarityn)
- fexofenadine (Afexil, Ewofex, Telfast)
- rupatadine (Tamalis)
- acrivastine
- ebastine
- terfenadine
- mizolastine