Histamine and antihistamines

Introduction Histamine is an endogenous substance, widely distributed in the body, also called "Autacoid" or local hormone, because it acts locally at the site of release.

1. Synthesis: is synthesized in the tissue from L-histidine by decarboxylation
2. Distribution: presents mainly in the skin, lung and gastrointestinal tissues, as these tissues are in direct contact to the outside of the body. It's also stored near blood vessels and in the CNS.
3. Release: histamine is usually released with other substances as serotonin, cytokines, leukotriens, prostaglandins and Platelets activating factors.

Factors stimulating histamine release:

1. Antigen-antibody (IgE) reaction on the surface of the mast cells and blood basophils (immediate hypersensitivity reaction), this will lead to activation of proteolytic enzymes and increase the influx of calcium to the inside of the cell causing cell degranulation and histamine release
2. Drugs induce release: drugs as morphine, codeine, d-tubocurarine and guanethidine can release histamine probably by displacement from its cellular binding sites.
3. Other substances as snakes and insects venom and radiation can release histamine

4. Metabolism: the released histamine is inactivated by histaminase (diamine oxidase) and by histamine methyltransferase enzyme present in various tissues.
5. Histamine receptors: three types of receptors include H1, H2, and H3

H1- receptors: mainly present in intestinal and bronchial smooth muscles (stimulation increases intracellular calcium).

H2-receptors: Gastric mucosa (stimulation increases cAMP)

H1+H2: the combination is mainly present in the blood vessels and

H3 : mainly in the CNS, it probably regulates histamine release

Physiological role:

1. Regulation of microcirculation in arterioles and capillaries
2. Control of gastric acid secretion
3. Neurotransmission
4. Mediation of pain and itching by affecting sensory nerve endings
5. Endocrine regulation and control of hormone release

Role in disease state:

- Allergic rhinitis (hay fever)
- Bronchial asthma
- Urticaria and eczema
- Contact dermatitis
- Food allergies

In all these diseases condition histamine is usually released in combination with other mediators

I. Pharmacological effects of histamine:

1. Cardiovascular system: histamine causes fall of blood pressure, has positive inotropic and chronotropic effects, causes flushing of the face (cutaneous vasodilatation). It also causes throbbing headache due to cerebral vasodilatation. The vasodilator effect of histamine is probably mediated by the release of nitric oxide (NO) from the endothelium of the blood vessels.

The dilation of capillaries by histamine lead to increase vascular permeability and tissue swelling

2. Respiratory System: Bronchial smooth muscle contraction mediated by H1 receptors stimulation, it also increases secretory activity and prostaglandins release.
3. Histamine causes increase in catecholamine release from the adrenal gland
4. Intradermal injection of histamine leads to red line due to vasodilatation, flare due to axonal reflex and wheal due to edema formation (triple response). Histamine injected locally also causes pain and itching due to irritation of sensory nerve ending
5. Anaphylactic reaction: Rapid and extensive release of mediators which may be fatal. Introduction of specific antigen usually in food or injected materials into sensitized individuals causes rapid release of mast cell contents. This leads to intense bronchospasm and severe hypotension which might cause death. All mediators involved in this reaction.

<u>Sodium cromoglycate (cromoglicate):</u>

Inhibits histamine release from mast cells, also reduce allergic reactions and bronchial hyper-reactivity. Useful in the prophylaxis of bronchial asthma. It is not absorbed when given orally, so it is given by inhalation. Also useful in allergic rhinitis by nasal drops.

II. **Antihistamines**

A. Classification:

1. H1- antagonists (blockers), also called conventional antihistamines, examples; chlorpheniramine, diphenhydramine, promethazine and cyproheptadine.

2. Non-sedating H1-antihistamines such as terfenadine, astemizole and loratadine
3. H2-antagonists: as cimetidine, ranitidine and famotidine

I. H1-antanonists:

Examples; diphenhydramine, chlorpheniramine, cyclizine and promethazine are receptors blocking agents compete with histamine at H1 receptors, they have no effect on histamine release

A. Pharmacokinetics:

Are well absorbed when given orally with a peak plasma level at about 1 hour following ingestion.They are metabolized by the liver with a half-life of 3-4 hours

B. Clinical uses:

1. Allergic conditions; as allergic rhinitis and urticaria,
2. Motion sickness; antihistamines as diphenhydramine and cyclizine are effective in the treatment of motion sickness probably due to their anticholinergic effect, which cause reduction of fluid in the inner ear
3. Diphenhydramine is useful in the treatment of Parkinson's disease again due to its anticholinergic effect
4. Sedation, most of these drugs have a potent sedative action, this can be useful in the treatment of anxiety associated with allergic diseases, and on the other hand excessive sedation can be considered as an adverse effect.
5. Anaphylactic shock :usually antihistamines are given in combination with other drugs such as adrenaline and corticosteroids
6. Antihistamines are not useful in bronchial asthma due to the anticholinergic effects

C. Adverse effects

1. sedation, drowsiness, dizziness fatigue, tremor and nervousness
2. Antimuscarinic effect; which lead to dryness of mouth, blurring of vision , retention of urine
3. others as agranulocytosis

II. Non-sedating antihistamines:

Examples: terfenadine, fexophenadine, astemizole, cetrizine and loratadine

These are characterized by:

1. Non-sedating as they do not pass the blood brain barriers
2. lacking anti-musacrinic adverse effects:

Terfenadine has cardiac toxicity characterized by ECG changes as prolongation of QT interval, this toxicity is potentiated when given with enzyme inhibitor drug as erythromycin and ketoconazole

III. H2- receptor antagonists:

Examples: cimetidine, ranitidine, famotidine and nizatidine

They act by selectively binding to H2 –receptors in the stomach. They reduce hydrochloric acid secretion by gastric mucosa, they can reduce the volume of acid secretion and also modify its PH (causes increase in PH).

Both effects promote the healing of peptic ulcer.

1. Cimetidine:

Is the prototype of the group, it is useful in the treatment of peptic ulcer (both duodenal and gastric ulcers).

Cimetidine is well absorbed when given orally, with peak blood concentration reaches in 1 hour.

Adverse effects:

1. Headache, dizziness, drowsiness and tremor
2. lethargy, fatigue , confusion and hallucinations specially in the elderly
3. Gynaecomastia also occurs due to the anti-androgenic effect of cimetidine
4. Cimetidine is an enzyme inhibitor, it inhibits CYP450 types(CYP 1 A2 and CYP 3A4), therefore it may increase the serum levels of some drugs such as phenytoin, warfarin and theophylline.