ORGANIC NITROGENOUS COMPOUND INVOLVED IN LOCAL IMMUNE RESPONSES

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ABSTRACT
Histamine is the major cause of allergy, urticaria, common cold, Hay fever, food allergy, and rhinitis. In today’s life it is necessary to know about the factors that increases histamine level in the body such factors are histamine containing food or food that inhibit the enzyme diamine oxidase. Stress is an another important factor that influence the histamine level in the body and that drugs that increases the histamine level in the body .The first generation antihistaminic drugs have certain side effects but also have some special property for example-promethazine is used to control pregnancy vomiting, sialorrhoea, tremor, morning sickness and cyproheptidine is having appetite stimulant activity. The first generations antihistaminic drugs are also available in the market the main cause of it is the muscarinic receptors activity of the first generation activity. The second generation antihistamines overcome the side effects that were caused by the first generation antihistaminic drugs mainly sedation. The second generation antihistaminic have a disadvantage that they are less effective to common cold, rhinitis due to lack of muscarinic activity. The second generations drugs (cetirizine) have property to inhibiting leukotriene C4 and D4 that are main cause of asthma The future aspect is to control the release of histamine in the body by H3 antagonists. The H3 antagonists also have antidepressant activities that overcome the stress factor.

KEYWORDS:

• INTRODUCTION
Histamine is a biological active substance found in a great variety of albeit unevenly throughout the animal kingdom and is present in many plants and bacteria and in insect venom. Histamine is a chemically classified as an amine, an organic molecule based on
structure of ammonia. It is formed by the decarboxylation (the removal of a carboxyl group) of the amino acid histidine.

English scientist George Burger and Henry H. Dale first isolated histamine from the plant ergot in 1910 and in 1911, they isolated the substance from any tissues. Plants that produce histamine stinging nettles; the histamine in the hair liked substance on nettle leaves is partly responsible for the swelling and the itching.

Histamine is also the irritating ingredient present in the venom of many species of wasps and bees. In human histamine was found in nearly all tissues of the body, where it is stored primarily in the granules of tissue mast cells. The blood cells called basophiles also harbor histamine-containing granules. Once released from its granules, histamine produces many varied effects within the body including the contraction of smooth muscle tissues of the lungs, uterus, stomach; the dilation of blood vessels which increases permeability and lowers blood pressure; the stimulation of gastric acid secretions in the stomach and the acceleration of heart rate. Histamine also serves as a neurotransmitter carrying chemical messages between nerve cells.

The effect of histamine has on blood vessels is crucial to its role in the immune response, which is most clearly observed in inflammation i.e. the local reaction of bodily tissues to injury caused by physical damage, infection or allergic reaction. Injured tissue mast cells release histamine, causing blood vessel to dilate and increase in permeability. This allows fluid and cells of the immune system such as leukocytes and blood plasma proteins, to leaks from the bloodstream through the vessel walls and migrates to the site of tissue injury, where they begin to fight the infection and nourish and heal the injured tissues.
In allergic reaction – the immune systems hypersensitivity reaction to usually harmless foreign substances (called antigens in the context) that enter the body – mast cell release histamine in inordinate amounts. Immune system proteins called antibodies, which are bound to mast cells, but in the process, the mast cells are stimulated to release their histamines. This causes the visible symptoms of a localized allergic reaction including runny nose, including runny nose, watery eyes, constriction of bronchi and tissue swelling. Histamine also contributes to generalized allergic conditions anaphylaxis a serve immediate and often fatal response to exposure to a previously encountered antigen.

**HISTAMINE AND THEIR RECEPTORS**

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Location</th>
<th>Type</th>
<th>Effect</th>
<th>Treatment</th>
<th>Agonist</th>
<th>Antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1</td>
<td>Smooth muscle, endothelial, heart, CNS.</td>
<td>G-protein linked to intracellular $G_q$.</td>
<td>Increase vascular permeability at inflammation.</td>
<td>Allergies, nausea, sleep disorder.</td>
<td>2-methyl-histamine.</td>
<td>Cetirizine, Meclizine, Buclizine</td>
</tr>
<tr>
<td>H2</td>
<td>Gastric parietal cell, neutrophiles, heart, CNS.</td>
<td>G-protein linked to intracellular $G_q$.</td>
<td>Increase release of gastric acid.</td>
<td>Stomach ulcers</td>
<td>4-methyl-histamine</td>
<td>Ranitidine, Famotidine, Cimetidine, Nizatidine</td>
</tr>
<tr>
<td>H3</td>
<td>CNS (thalamus, cortex), intestine</td>
<td>G-protein linked to intracellular $G_i$.</td>
<td>Release histamine.</td>
<td>Unknown</td>
<td>Alpha-methyl-histamine</td>
<td>Thioperamide, Ciproxiam, Clobenpropit</td>
</tr>
<tr>
<td>H4</td>
<td>Immune system e.g. spleen, thymus</td>
<td>Unknown but may be G-protein coupled.</td>
<td>Unknown</td>
<td>Autoimmune diseases</td>
<td>N-methyl-histamine</td>
<td>JNJ-777777-120</td>
</tr>
</tbody>
</table>

**HISTAMINE AND ITS RELATION TO STRESS**

Histamine acts as a neurotransmitter and in brain, it plays a many of physiological roles. Histamine release and its action have quite in relationship with each other.

Where acute stress increases the histamine turnover in the diencephalon and the striatum. Histamine release increase due to anxiety that is why anti-anxiety drugs decreases the brain
histamine turnover, where the H1 antagonist and H3 antagonist also decreases the histamine anxiety status.

The chronic stress continues to the nucleus accumbens and striatum but not in diencephalon. Moreover, H3 antagonists have antidepressant action.

• **FOODS INCREASE HISTAMINE LEVEL IN THE BODY**
Foods that increase histamine level in the body are mainly pasteurized milk, fish, cheese, fruit juice, fermented vegetable, tomato, sausage, vinegar, chocolate, meat, and mushroom. These substance increase histamine level in the body by inhibiting the enzyme diamine oxidase due to which histamine failed to break into imidazole acetic acid.

• **HISTAMINE AND STRESS**
Histamine release is a sensitive indicator of stress and chronic resistance or metabolic stress are among the most potent activators of histamine neuron. Histamine neurons respond to immobility, foot shock, hypoglycemia and dehydration. Histamine mediates the stress-induced neuroendocrine hormone surges of ACTH, beta-endorphin, and AVP from the pituitary and controls stress related activity of aminergic systems, including serotonin, norepinephrine, dopamine and acetylcholine containing neurons. As an integral part of the neural networks generating autonomic patterns histamines neurons interfere with AVP and sympathetic command neurons in the PVN to influence sympathoadrenal outflow, cardiovascular, stress related behaviour such as flight-fight or grooming.

• **HISTAMINE INTOLEANCE TEST**
Prick-testing with 1%histamine solution and wheal size-measurement to assess the relation between the wheal in prick-test, read after 20 to 50 minutes, as sign of slowed histamine degradation as well as history and symptoms of histamine intolerance.
• CHARACTERISTIC OF HISTAMINE BLOOD LEVEL

Blood histamine normal 25-65ng/ml

low blood histamine (histapenia)--paranoia, overstimulation: low productivity, excessive need for sleep, high tolerance for pain, low tolerance for drugs, low libido; slow sexual response, easy frustration, few allergic reactions, non-addictive nature, slow metabolizer of food, tension, headache.

high blood histamine (histadelia)--obsession and compulsion, overstimulation, less than average need for sleep, low tolerance for pain, low tolerance for drugs, high libido; fast sexual response, exaggerated depression, frequent allergic reaction, high addictive potential, rapid metabolizer of food, migraine-type headache, muscle-spasm syndrome.

• HISTAMINE ANTAGONISTS

Forneau and Bovet, who observed that piperoxan protects guinea pig against histamine-induced bronchospasm, discovered the first antihistamine.

Piperoxan has also important effects related to nor-epinephrine.

• THE FIRST GENERATIONS H1 ANTIHISTAMINES

The first generation antihistamines are useful in effective treatment of allergic responses such as—Urticaria, hay fever, rhinitis, food allergy, and common cold and as sedative and anti-anxiety.

<table>
<thead>
<tr>
<th>HIGHLY SEDATIVE</th>
<th>MODERATELY SEDATIVE</th>
<th>MILD SEDATIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphenhydramine</td>
<td>Meclizine</td>
<td>Chlorpheniramine</td>
</tr>
<tr>
<td>Dimenhydrinate</td>
<td>Pheniramine</td>
<td>Clemastine</td>
</tr>
<tr>
<td>Promethazine</td>
<td>Cyproheptidine</td>
<td>Tropolidine</td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td>Cinnarizine</td>
<td>Cyclizine</td>
</tr>
</tbody>
</table>
Many first generation antihistamine antagonize muscarinic action can be graded as HIGH MUSCARINIC ACTIVITY or LOW MUSCARINIC ACTIVITY:

<table>
<thead>
<tr>
<th><strong>HIGH MUSCARINIC ACTIVITY</strong></th>
<th><strong>LOW MUSCARINIC ACTIVITY</strong></th>
</tr>
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<tbody>
<tr>
<td>Promethazine</td>
<td>Chlorpheniramine</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>Hydroxyzine</td>
</tr>
<tr>
<td>Dimenhydrinate</td>
<td>Tripolidine</td>
</tr>
<tr>
<td>Pheniramine</td>
<td>Cyclizine</td>
</tr>
<tr>
<td>Cyproheptidine</td>
<td></td>
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</tbody>
</table>

**SPECIAL EFFECTS OF FIRST GENERATION ANTIHISTAMINIC**

- Promethazine - control vommiting of pregnancy
- Reduce tremor, sialorrhoea
- Motion sickness, morning sickness
- As a local anaesthetic cause irritation
- Cyproheptidin –As apeetite stimulant (off-label drug)

**ADVERSE EFFECTS OF FIRST GENERATION ANTIHISTAMINE**

- Cross blood brain barrier so cause drowsiness
- Tachycardia
- Blurred vision
- Urinary retention
- Constipation
- Somnolence
- Decreased cognitive ability
- Weight gain

Note-Many of its side effect is due to its anti-cholinergic action of the drugs.

**THE SECOND GENERATION ANTIHISTAMINIC DRUGS**

The second generations drugs are have some qualities that make them superior to the first generation antihistaminic

Absence of CNS depressant property
Higher H1selectivity- No cholinergic effects
Additional ant allergic mechanism—some drugs of second generation inhibit leukotrienes (C4, D4) and platelet activating factor (PAF). Cetirizine is having this kind of mechanism.

**FEXOFENADINE**

Fexofenadine is from the group of terfenadine, astemozole, cisapride, and grepafloxin. Only fexofenadine is in markets now a day. Where all the other drugs from the group were no
longer marketed due to their dangerous cardiac arrhythmic action occurs when the drug is taken in high concentration or with CYP3A4 inhibitors such as ketoconazole or macrolide antibiotics (Triacetyloleandomycin). These cardiac effect associated with blockade of the HERG (human ether–ago–go) gene product that delay rectify K⁺ channel. Where Fexofenadine have low potency to delay the blockade of the K⁺ channel.

**LORATADINE AND DESLORATADINE**

Loratadine is related to the first generation antihistamines and to antidepressant. Loratadine has a major advantage that it does not interact with antifungal drugs and macrolides.

- Desloratadine- It the major active metabolite of loratadine. It is more potent inhibitor of histamine release. It has interfered with psychotic performance.

**CETIRIZINE AND LEAVOCETIRIZINE**

Cetirizine is an acid metabolite from oxidation of primary alcohol of histamine hydroxizine, is a widely used selective for H1 receptors. Cetirizine has no cardiotoxicity but some drowsiness occurs.

Leavocetirizine- Leavocetirizine has higher affinity than S-enantiomer for the H1 receptor and is more slowly distributed.

**ACRIVASTINE**

Acrivastine is acidic congener of tripolidine in which a carboxylic acid –substituted carboxylic chain has been attached. It is principally in a combination with a decongestant.

**EBASTINE AND CAREBASTINE**

Ebastine, which is structurally similar to Terfenadine, is a potent selective H1 antihistamine free from anti cholinergic effects sedative action.

Carebastine blocks the release of PGD2 and leukotriene C4/D4 in cellular assay.

**TOPICAL H1 ANTIHISTAMINES**

Antihistaminic drugs are also available for the topical application on the body there are a few H1 antihistaminic drugs such as olopatadine, levocabastine, emedastine, azelastine, ketofien, epinastineqq are available for topical use.

**REFERENCES**