



endocrine SYSTEM



Pharmacology

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Autacoids

Sometimes are called local hormones, as you know hormones work systematically, but these substances work locally at the site of their release, they are not neurotransmitters, not real hormones, they are a unique group of substances with different actions. Pharmacologically, they can be affected by some drugs that modify their results. Collectively, they are called **Autacoids** and defined as:

Endogenous substances with complex physiologic and pathphysiologic functions; commonly understood to include Histamine, Serotonin, Prostaglandins, Vasoactive peptides and maybe many others, but we are going to discuss only histamine and serotonin in this lecture.

*They are important for the normal physiology of the body as well as the pathophysiology of many conditions like allergy and bronchial asthma.

*Histamine maybe was the first one to be labeled as Autacoid then the list was enlarged by the addition of the Serotonin and Prostaglandins.

*Prostaglandins were known 40-50 years ago, while histamine 70-80 years ago. Much different from Ach, Norepinephrine and Epinephrine which were known 100 years ago, and different from Insulin which was known in 1921.

Histamine

*Occurs in plants, animals, venoms, and stinging secretions. **They are widely available in nature not only in humans.**

***Formed from l-histidine**, which is an aromatic amino acid.

***Mediator of immediate allergic and inflammatory reactions.** Inflammatory reactions include bronchial asthma, arthritis and other autoimmune diseases while allergic reactions include various antigens which the human body is exposed to.

Plays only a **modest role in anaphylaxis.*

NOTE* *What is the difference between prophylaxis, anaphylaxis and allergy? The doctor didn't mention this point but I thought it is helpful for more understanding. The similarity in names is misleading. Prophylaxis is anything (drug or vaccine) that is given prior to an incident in anticipation of a potential mishap. Anaphylaxis is a severe immune reaction to any drug or chemical - even biological which leads to instant shock and possibly death if untreated so anaphylaxis is part of the immune complex; it's one of the allergic reactions but classified as class 4 immediate types of allergic reactions.*

*Importantly involved in **gastric acid secretion** as we took in GI course.

***Neurotransmission** in certain sites in the CNS.

***Stored in granules in mast cells and basophiles, and inactivated.** As you know mast cells and basophiles are involved in the allergic as well as the inflammatory reactions. Once formed, it is either quickly inactivated or stored.

There are **two types of release** according to the stimuli:

1-Immunologic Release:

IgE and antigen interaction causes explosive degranulation of the mast cells and release of histamine, ATP, and other mediators, which contribute to the allergic reaction.

2-Chemical and Mechanical Release:

Drugs like morphine and tubocurarine (skeletal muscle relaxants that cause side effects like hypotension, bronchospasm due to histamine release).

Scratching your skin is a mechanical stimulation that result in destruction of the mast cells under the skin.

➤ **Molecular actions of histamine**

Histamine works through G Protein Coupled Receptors: H1, H2, H3, H4 types, that have no subfamilies. There is no H1a or H1b, although the field of receptors science recently enlarged to identify very minor differences in receptors that are labeled as subfamilies.

H1 and H2 receptors are the most common:

1-Activation of **H1 receptors**. It works in this receptor **through** the liberation of the **IP3**.

Found mainly:

A-In endothelium causes vasodilation.

B-In smooth muscle cells in GIT causes contraction.

C-In nerve endings in the CNS.

Partially selective agonist: Histaprodifen

Partially selective antagonist: Mepyramine, Triprolidine and Tetirizine

2-Activation of **H2 receptors**. Through cAMP

Found mainly in: gastric mucosa, cardiac muscle, and some immune cells.

Partially selective agonist: Amthamine.

Partially selective antagonist: Cimetidine, Ranitidine and Tiotidine.

NOTE* *What is the difference between selectivity and specificity? Selectivity: prefer working on H1 receptor and still can work on H2 receptor but with less activity. Specificity: working on H1 receptor only.*

➤ **Pharmacologic Effects of Histamine:**

***Satiety effect.** So the use of anti-histamine drugs increases the appetite.

***Decrease BP and increase HR.** decreasing the BP causes an elevation of the HR as a stimulation of the baroreceptor reflex happens.

***Constricts bronchial muscle.** And this is evident in bronchial asthma.

***Stimulates GI smooth muscle.**

***Stimulates gastric acid secretion.**

***Triple Response:** intradermal injection causes red spot, edema, and flare response. It is the same response caused by scratching a light-colored skin.

***Pain sensation** in the peripheral tissues.

NOTE* physiologically, histamine is very important, but it is not used pharmacologically because giving histamine for its satiety effect for example will cause many side effects including increased acidity, decreased BP ...etc. so histamine and histamine agonists are just used for experimental purposes.

➤ **Histamine Antagonists**

1-Physiologic Antagonists: not a receptor blocker and work immediately in an opposite fashion to histamine.

Epinephrine

While the main effects of Histamine are vasodilation and bronchoconstriction, the main effects of Epinephrine are vasoconstriction and bronchodilation; so Epinephrine is

considered as very useful **antidote** for histamine and as a life-saving measure **treatment of anaphylactic shock** (which is zero blood pressure with bronchoconstriction and it may be caused by the release of histamine or other mediators).

2-Release Inhibitors: drugs that can inhibit the release of Histamine; so it is used before the release. ***They are used prophylactically.***

Example: prophylactic treatment of bronchial asthma (bronchial asthma patient when he wants to climb the stairs he knows that climbing the stairs will cause a bronchial attack so before climbing he takes a release inhibitor).

Cromolyn and **Nedocromil**

3-Receptor Antagonists: these drugs will compete with histamine on its receptors; competitive inhibitors usually are reversible.

→H1 receptor antagonists

*Known long time ago, 60 years.

*Used in the **treatment of allergy**. Skin, eye, nose and other allergies.

*Available without a prescription (**Over-the-counter drugs**) due to the safety of these drugs.

*Available **alone, or in combinations** such as "**cold preparations**" which are associated with allergic reaction, other than the infection itself, caused by the release of histamine, and "**sleep aids**" because it causes sleepiness or sedation as a side effect.

NOTE* Common cold or flu or URTI: Antipyretics to reduce the temperature +Analgesics to reduce the pain +Antihistamines to reduce the allergic reaction.

❖ H1 receptor antagonists are divided into:

1-First Generation: old-fashioned

-Strong sedatives because they can cross BBB. It could be a dangerous side effect for drivers or students, but it can be used to make children more than 6 months go to sleep.

-Have autonomic α & M blocking effects as well as H1 receptor, they have many side effects due to its non-selectivity as other old drugs, so it's not preferred because it's not safe.

Examples: **Diphenhydramine, Chlorpheniramine.**

2-Second Generation:

-Less lipid soluble, so **no or less sedative activity**.

Examples: **Fexofenadine, Loratidine and Cetirizine**.

❖ Pharmacodynamics of H1 Antagonists:

*Sedation:

-Very common with **first generation agents**.

-**Varies among agents and patients**.

-**No abuse potential**. Most of the sedative agents cause addiction but not these agents due to the blocking of alpha and M receptors which has effects such as dryness, tachycardia high temperature, decrease sweating, weakness and hypotension; so you won't be addicted to such effects.

-**Cause stimulation and convulsions at high doses**. So it's contraindicated in infants of 6 months or younger.

***Antinausea and antiemetic**. Related to M blocking.

***Antiparkinsonism**. Due to its central action.

***Anticholinergic**.

***Alpha blocking**.

***Serotonin blocking**.

***Local anesthesia**.

❖ Clinical uses of H1 Antagonists:

1-Allergic reactions:

-More effective when given before exposure.

-Sedative effect reduces awareness of itching.

-Local application may induce allergy by itself. So you should give it orally or IV.

2-Motion Sickness and Vestibular Disturbances (Menier's Syndrome) which happens due to sclerosis of the blood vessels in the inner ear at old age.

3-Nausea and vomiting of Pregnancy (Morning Sickness)

-Teratogenic in rodents. So they are not advisable for the treatment during pregnancy, there are better drugs.

→ H2 receptor antagonists

*Breakthrough **treatment for peptic ulcer disease** (1972). Before 1972 the only treatment was surgical removal due to the fact that the only drugs that were available are anti-acid drugs that only neutralize the acidity, but do not heal peptic ulcer.

***Do not completely abolish acid secretion**, they reduce acidity by 40-60% while anti-cholinergic drugs (atropine-like drugs) can reduce acidity 20-30%, it has many side effects and it's not effective.

But Nowadays, H2 receptor antagonists are replaced by **proton pump inhibitors (100% inhibition)**. PPIs, like omeprazole, were discovered in 1990s, they are very effective as you see but they cause renal impairment; so it is not advisable to use them *continuously*.

Examples of H2 receptor antagonists: Cimetidine (the prototype), **Ranitidine, Famotidine** and **Naziditine**.

Serotonin or 5-Hydroxytryptamine or 5-HT

Serotonin: a vasoconstrictor released from the blood clot, it helps in closure of vascular injury.

Enteramine: a smooth muscle stimulant found in intestinal mucosa.

*Later they discovered that these two substances have the same chemical structure which is 5-Hydroxytryptamine (synthesized in 1951).

***Widely distributed in nature**, found in plants (Banana), animal tissues, venoms and stings.

***Synthesized from L-tryptophan**.

***Stored, or rapidly inactivated by MAO**.

***90% is found in the enterochromaffin cells of the GIT, also found in platelets, enteric nervous system, nerve endings, and brain.**

*Involved in mood, sleep, appetite, temperature control, pain perception, depression, anxiety and migraine.

*There are 5-HT₁, 5-HT₂, 5-HT₃, 5-HT₄, 5-HT₅, 5-HT₆ and 5-HT₇ receptors, and unlike histamine, it has many **different subfamilies** and different post-receptor mechanisms.

➤ Pharmacologic Effects of Serotonin

→Nervous System:

*5-HT is converted to **Melatonin** in the brain which contributes in **sleep mechanism**.

***Chemoreceptor Reflex** (Bezold-Jarish Reflex): activation of 5-HT₃ receptors in coronary arteries, leads to hypotension and bradycardia.

→Respiratory System:

***Bronchoconstriction** and **hyperventilation**.

→Cardiovascular System:

***Vasoconstriction**. Generally speaking

***Vasodilation** in skeletal muscles and coronary arteries, intact healthy endothelium is required. When endothelium is not intact (unhealthy), might be caused by atherosclerosis, you won't find serotonin and there will be no vasodilation.

***Platelets aggregation**. Consequently, platelets destruction will lead to the release of serotonin and this will cause vasoconstriction in an attempt to reduce the vascular injury and to initiate the process of clot formation and reduction in bleeding.

→GIT:

***Stimulation and diarrhea**. Stimulation means abdominal pain and contraction of GIT and increased secretions.

***Carcinoid Syndrome**: due to a tumor of the enterochromaffin cell, sometimes in pancreas.

→Skeletal Muscle:

***Serotonin Syndrome:** due to **excess serotonergic activity, potentially fatal, skeletal muscle contraction and hyperthermia, predictable not idiosyncratic.**

➤ **Clinical Uses of Serotonin and serotonin agonists**

Serotonin itself has no clinical application because it works on all 5-HT receptors. But its selective agonists are of clinical importance.

***Buspirone:** (5HT_{1A} agonist)

Anxiolytic activity, nonsedating. Most drugs that are used in the treatment of anxiety usually cause sedation, but this drug does not, and this is an added value.

***Triptans:** e.g. **Sumatriptan** (5HT_{1D/1B} agonists)

First line drugs for migraine headache. You know headache could be vascular or inside the skull (increased intracranial pressure for example), but migraine is a severe *vascular* type of headache caused by vasodilation, so this drug causes vasoconstriction.

***Cisapride\ Tagaserod:** (5HT₄ agonist)

Used only in gastroesophageal reflux disease GERD, which is a very common problem, this drug will enhance GI motility normally rather than retro.

***Fluoxetine:** (SSRI)

Widely used in depression, SSRI stands for serotonin selective reuptake inhibitor, it doesn't work on specific receptors but it inhibits the reuptake of serotonin to the neurons, so it will stay in the synaptic space and work in the receptors over there, which in turn controls the mood and treats depression (serotonin levels will increase in the brain).

This drug is considered a modern treatment of depression like schizophrenia, which is very serious problem because the old treatment depended on very toxic drugs, called tricyclic anti-depression drugs, they prevent reuptake of Serotonin and Norepinephrin and maybe other mediators, which causes serious side effects. SSRIs are selective and safe drugs, their discover in 1987 was a breakthrough in the treatment of depression.

NOTE* 1941 was breakthrough in the treatment of infectious diseases.

1971 was breakthrough in the treatment of peptic ulcer.

➤ **Serotonin Antagonists**

***Phenoxybenzamine**: (An old alpha blocker, but also 5-HT blocker).

As other old drugs, its **non selective** so it's not used.

***Cyproheptadine**: (5-HT₂ and H₁ blocker).

Useful in carcinoid and serotonin syndrome.

***Ketanserine**: (5-HT₂ blocker).

Antihypertensive agent. It is a new-class treatment of hypertension.

***Ritanserine**: (5-HT₂ blocker)

Prevents platelets aggregation. But to inhibit platelets aggregation, simply you can use Aspirin.

***Ondansetron**: (5-HT₃ blocker)

The most effective drug used to **prevent nausea and vomiting of cancer chemotherapy.**

Good luck