The Endocrine System

PHARMACOLOGY

☑ Sheet ☐ Slide ☐ Handout

Number:	1
Subject:	Autacoids/ Histamine
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(Slides, record sec.2)

For the upcoming lectures in endocrine pharmacology one of the main subjects that we will focus on is : Autacoids.

What are Autacoids? they are Local hormones , In Greek "Autos" (self) and "Acos" (relief, i.e. drug) .

**It is really the only place to talk about autacoids during our “medical school life”.

The reference is Katzung medical pharmacology book.

13th edition (271-286), 12th edition (273-287)

Case study

The doctor fabricate this story for us. A Family went to Zayy, a Jordanian park, for picnicking one of them get a bee-bite, he shouted. They moved him to the hospital after showing: difficulty to breathe and sever pain. As they reach the hospital, he collectively has: respiratory depression, rash all over the body, very low blood pressure. Fortunately, they could manage the case at the hospital. However, the family said that he has got bitten by a bee before, but he did not show these signs by then.

Analysis

The patient had anaphylactic shock, or let us say he had a severe allergic rxn. The body recognize the antigen (that he got from the bee- bite) from a previous exposure and the type of rxn is humoral, which means that it is mediated by an antibody to be more specific: IgE antibodies. So it is IgE mediated hypersensitivity.

More details: when he got bitten first time a foreign antigen enter his blood sequentially, memory cells were made, these memory cells produce IgE antibodies as an antigen from the same type re-enter, when this happen an antigen-antibody rxn occur on the surface of mast cells, granulated cells, which leads to mast cells’ degranulation, this will release the granules contents. (Refer to fig. 1)

These granules contain:

- ✓ **Histamine**
- ✓ Serotonin
- ✓ Proteases
- ✓ Neutrophils & Eosinophil chemotactic factor
- ✓ Leukotrienes & Prostaglandins
- ✓ Bradykinin.

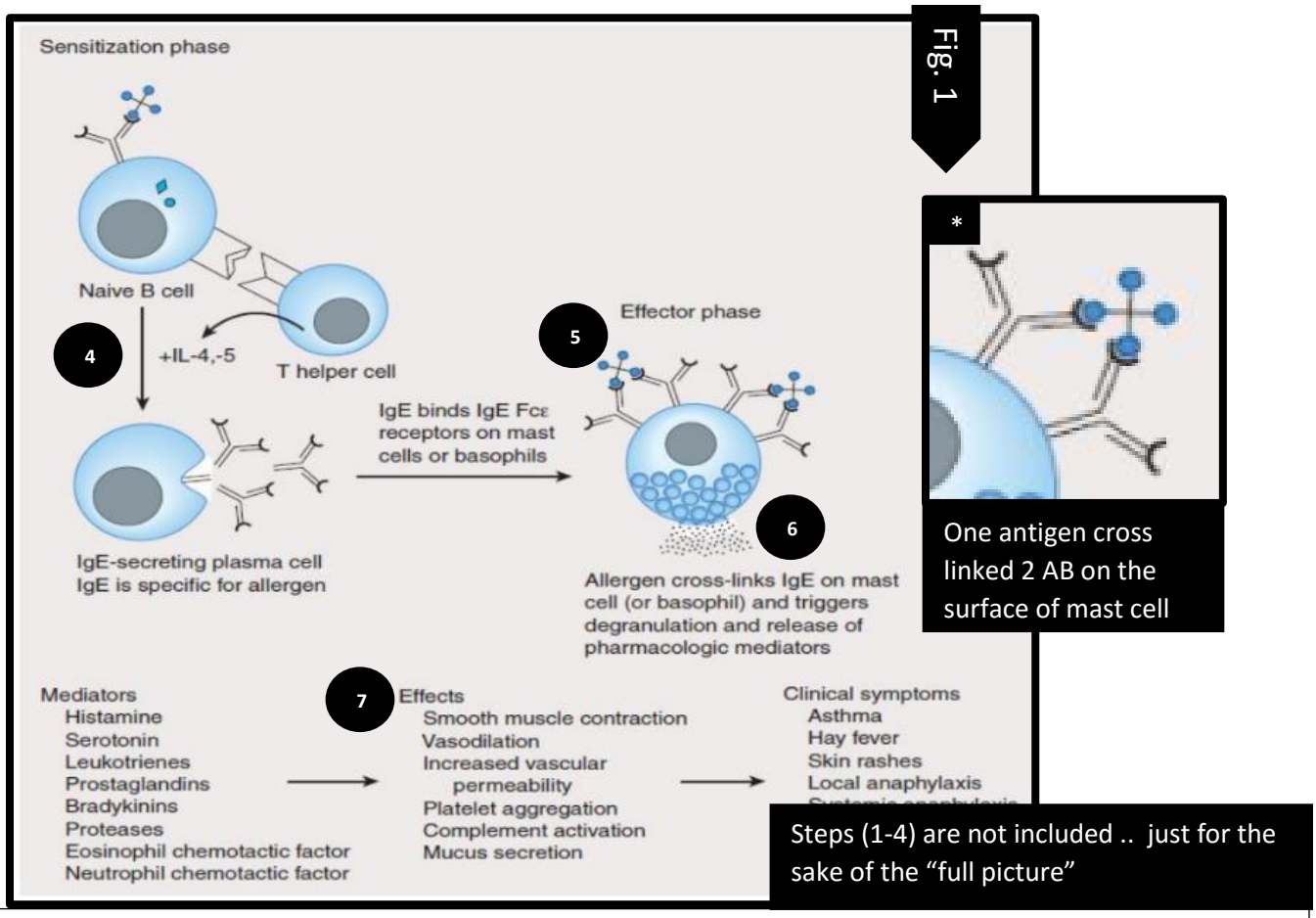

Fig. 1: IgE mediated allergic response

1. Foreign Antigen enter the body and get presented by dendritic cells (or any presenter cells)
2. Native T cells recognize the presented antigen
3. Native T cells differentiate into T helper cells that secret cytokines (like IL-4 /13)
4. cytokines stimulate b cells to produce IgE and memory cells are produced
5. When the same antigen re-enter IgE bind its receptor on mast cells and an antigen-antibody rxn occurs, notice how one antigen cross two AB indicated as (*)
6. Degranulation of mast cells and release of histamine and other mediators
7. histamine produce its effects

The release of histamine could also be mediated by IgM and IgG, these will activate complement cascade and will also release histamine from mast cells and basophiles. However, IgE mediated histamine release is the most common. (We will talk further about histamine release later in this sheet)

Conclusion

Histamine (and other mediators) led to the signs that appeared on this patient. (Bronchoconstriction, low BP, Pain...)
In order to Know what the doctors do to manage this case, we must study Histamine: Pharmacological action, therapeutic uses, agonists & antagonists..

Notice that we over simplified things here, as histamine do not work alone but work with other mediators, for example bronchoconstriction is mediated by histamine, bradykinin, LTs & some PG .

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Functions of histamine

Histamine is:

- ✓ An important autacoid, it acts **locally** (at the site of release).
- ✓ Mediator of allergic rxn.
- ✓ Stimulant of gastric acid secretion in stomach.
- ✓ Neurotransmitter and neuromodulator at CNS. [if u are interested in Knowing the difference between neurotransmitter and neuromodulator, press here]
- ✓ Immunity reagent.
- ✓ Chemotactic of neutrophils.

In addition, Histamine is present at many plants and animals (at their venoms). When a plant stings you, you will feel pain and itching due to its histamine-rich-bite.

Pharmacokinetics

Histamine has two hits, either being stored or destroyed (rapidly inactivated); after decarboxylation of the amino acid histidine, histamine is produced and stored in granules (in 1) mast cells or 2) basophils or 3) synaptic vesicles in CNS..) then when it's the right time and the right place it get released, histamine does not circulate to far places like ACTH for example, because it is an Autacoid (act locally).

It is notable to mention that

- ✓ If you wanted to monitor the level of histamine in a tissue, you measure the amount of mast cells and basophils in it (Histamine level in a tissue is proportional to the amount of mast cells and basophiles in that tissue).
- ✓ The histamine presented in the granules is not active, it is sequestered (need to be activated).
- ✓ Mast cells concentrate at pressure points (EX: at a foot that you are standing on) or sites of bifurcation (ex: when an artery bifurcate into two) sites of potential injuries (ex: nose, mouth, and feet) and internal body surfaces.
- ✓ Several tumors are rich in mast cells and histamine: 1) systemic mastocytosis, 2) urticaria pigmentosa, 3) gastric carcinoid and 4) myelogenous leukemia

Note generally all carcinoid tumors are rich in Histamine. We mentioned gastric carcinoids specifically to highlight that histamine enhances acid secretion in stomach which lead to multiple thick peptic ulcers.

Non-Mast cells histamine

We mean by non-mast-cells histamine, histamine that is not stored in neither mast cells nor basophils, and it is present in:

- ✓ Synaptic vesicles of CNS.
- ✓ Stomach Enterochromaffin-like cells.

Functions of Non Mast cells Histamine (mentioned in slides only)

• In the brain, it functions as a neurotransmitter, and plays a role in neuroendocrine control, cardiovascular regulation, thermal and body weight regulation, and sleep and arousal.

• In enterochromaffin-like (ECL) cells of the fundus of the stomach, it is involved in activation of the acid-producing parietal cells of the mucosa.

Release and storage of histamine +Regulation

In fig. 1 we explain how IgE mediate histamine release. And we said that histamine could also be IgM and IgG. What I want to add here that the Immunologic release of histamine requires energy and Ca^{++}.
Furthermore, we pin point that histamine is trapped inactively inside its granules.
Does it kept without **regulation**?

No (!), histamine like many other mediators is tightly regulated by negative feedback control; which means that histamine is regulated by itself through H2 receptors. However this regulation occur in basophiles and skin mast cells <u>but not in lung mast cells.</u>

Pharmacological effect

Endogenous histamine modulates a variety of inflammatory and immune responses:

- ✓ **Local vasodilation and increased vascular permeability**: any capillary is surrounded by one layer of endothelium cells, when the blood vessel dilate the spaces between these cells increase, allowing the content of blood plasma to leak out.
  Things that may leak include mediators of acute inflammation (complement, C-reactive protein) and antibodies… this will mediate diseases (ex: ASTHMA)
- ✓ **Chemotactic attraction for inflammatory cells** (neutrophils, eosinophils, basophils, monocytes, and lymphocytes).
- ✓ **Inhibition of lysosomal content of B and T lymphocytes:** remember that lysosomal enzymes are destructive. This may be mediated by H2 or H4 receptors.
- ✓ **Release of peptides from nerves in response to inflammation**, these peptides cause pain, probably modulated by histamine acting on presynaptic H3-receptors.
  *H3 receptors mediate the negative action of histamine (Inhibitory) while the other H receptors are activators (of acid secretion and many other things)
  How come H3 are inhibitory and they <u>stimulate</u> nerve ending? Simply, inhibition of the inhibitor will lead to stimulation. So the signal mediated by H3 receptor Inhibit an Inhibitory function on these nerve endings, this activate them.

Chemical and mechanical release

Drugs that induce histamine release are not immunologic in nature but are chemical displacers. They displace histamine in its granules and produce the same effect of it. The magnitude of action is proportional to amount released. The rxn induced by these chemicals

are called anaphylaxis-like-rxn or allergy-like-rxn. These chemicals could be certain amines (morphine and tubocurarine) or even displacement by extracellular Na+.
**this process does not require energy and is not associated with mast cell injury or degranulation.

Pharmacodynamics

Mechanism of Action

Histamine Receptors

- ✓ histamine has four receptors (H1, H2, H3, H4); H stands for histamine :3 – also see table 1
  These receptors are coupled to G protein recall G protein/biochem
- ✓ Activation of H3 receptors decreases transmitter release from histaminergic and other neurons.
  for the sake of understanding this point we must stop at these two important concepts

Auto-receptors VS. Hetero-receptors

Nearly, pre-synaptically, all neurons have regulatory receptors that secret substances for the sake of regulation (inhibition) of release. Suppose I have a neuron that secret Ach, then if these neurons have Ach receptors that inhibit further release of Ach we call them auto receptors. Whereas if this inhibition where mediated by another substance (any substance but not Ach) like histamine we call these receptors hetero-receptors.
To sum-up auto receptors bind the same substance that I want to inhibit, while hetero binds a different substance.
So histamine could bind auto-receptors (H3) on neurons and inhibit its own release, or could bind hetero-receptors (H3) and inhibit other NTs release.

- ✓ H4 receptors have chemotactic effects on eosinophils and mast cells. So H4 induce further release of leukotrienes and other mediators from eosinophils, it may also induce further histamine release.
  By this we can conclude that: if there's an inflammation H4 receptors worsen things (more mediators), but H3 doesn't (Inhibitory).

Receptor Subtype	Distribution	Postreceptor Mechanism
H_1	Smooth muscle, endothelium, brain	G_q, ↑ IP_3, DAG
H_2	Gastric mucosa, cardiac muscle, mast cells, brain	G_s, ↑ cAMP
H_3	Presynaptic autoreceptors and heteroreceptors: brain, myenteric plexus, other neurons	G_i, ↓ cAMP
H_4	Eosinophils, neutrophils, CD4 T cells	G_i, ↓ cAMP

Table 1: histamine receptors (H1,H2, H3, H4) are G-protein coupled .notice how these G proteins varies (stimulatory , inhibitory , others) and how some receptors increase cAMP while others decrease it , other receptors work on IP3, DAG.*the doctor did not mention how these receptors are distributed however some are mentioned later>

Table 1

Organ System effect

Nervous system

- ✓ Stimulation of sensory nerve endings especially those mediating pain and itching (**H1**). Notice that it is important to know which receptor mediate each effect, in order to stop it by the suitable antagonist.
  So in order to stop pain and itching, we use H1 antagonists.
  <next lecture we will talk about agonist and antagonists of histamine in more details>
- ✓ Respiratory neurons signaling inspiration and expiration are modulated by H1 receptors.

- ✓ Presynaptic H3 receptors activation control transmitter release (acetylcholine, amine and peptide NTs) in the peripheral and central nervous systems. (Hetero-receptors Inhibitory H3 mentioned previously)

  There's a promising study that conclude that we could be able to use inverse H3 agonist (named: Pitolisant) used to treat narcolepsy patients. This drug is not approved yet.
  What is narcolepsy?
  Resistant desire for sleeping during daytime activities.
  They found that inverse H3 agonist would reduce drowsiness in patients with narcolepsy. (Drowsiness comes before sleeping, thus Pitolisant will reduce sleeping)
  Note: we know much more about H1 & H2 receptors than H3 & H4.

Appetite and satiety

- ✓ H1 and H3 receptors play important roles in appetite and satiety. If we block these receptors the patient will gain weight. This happen in Antipsychotic drugs as these block H1 & H3 and the patient weight increase.

Cardiovascular system

- ✓ Histamine mediate Vasodilation of arterioles and precapillary sphincters along with increased vascular permeability this will lead to reduction of blood pressure, flushing (redness of cheeks), sense of warmth and headache.
  - Why warmth? Histamine>>vasodilation>>more warm blood in the area >>warmth.
  (Notice that we said warmth not fever)
  - Why headache?
  When the vessel of the scalp (to be more specific the dura vessels, recall MSS) dilate they stretch the nerve endings surrounding them.

This will stimulate these nerves and eventually this produce pain (headache pain is Throbbing pain that increase with each pulse of blood as dilation increase and so on- زي الشاكوش المطرقة
like a hammer)

Mechanism of vasodilation (low VS. high doses):
Small doses of histamine produce vasodilation through H1 receptor activation which is mediated by nitric oxide release from the endothelium. While High doses of histamine activate H2 receptor and produce vasodilation by cAMP-mediated process.

- ✓ Tachycardia (increased heart rate) occur both directly (**H2**) and by reflex mechanisms*.
  * We will talk about reflux mechanisms in blood system. But in general baro-receptors include that if the blood pressure decrease heart rate will increase (tachycardia) and if the BP increase heart rate will decrease (bradycardia).
  [under the regulation of the sympathetic system]

- ✓ Edema Actions on post-capillary vessels (H1) leads to separation of endothelial cells and transudation of fluid and electrolytes and small proteins into the perivascular tissues. This effect is responsible for urticaria (hives/allergic skin rash), which signals the release of histamine in the skin.

Note: Some of the cardiovascular effects during anaphylaxis may be due to other factors (very important practically).

Respiratory/ Bronchial smooth muscle

- ✓ Histamine cause Bronchoconstriction mediated by H1 receptors.

Note: patients with bronchial asthma are 100-1000 times more sensitive to histamine. (Mentioned in slides only)

GI/Gastrointestinal smooth muscles

- ✓ Large doses of histamine contract GIT smooth muscle and may induce diarrhea (H1) by increase peristalsis.

Pregnancy

- ✓ Histamine may induce abortion. As it contract uterus muscles.

Secretory tissue

- ✓ Powerful stimulation of gastric acid secretion (H2), and to a lesser extent, of gastric pepsin and intrinsic factor production (for the absorption of vit. B12).
  A lot of people take H2 blockers if they have acidic reflux (esophageal reflux) to decrease stomach acid secretion. But H2 blockers also suppress vit. B12 that's why worldwide, up to 40% of the population are vit. B12 deficient.
- ✓ Histamine also stimulates secretion in the small and large intestine.
- ✓ H3 receptor activation inhibit gastric acid secretion.

Metabolic effects

Gene knock-out trial: When knocking out (suppress/delete/damage) H3 receptors gene in a mice they noticed the following: increased food intake, decreased energy utilization, and obesity. Obesity induce insulin resistance which leads to increased insulin levels leading to hyperinsulinemia and more obesity. Leptin also increases (produced by fat cells to suppress appetite, but in this case [obesity] there is leptin resistance)

we can conclude that H3 receptors are anti-obesity (we can not jump to such conclusion that easily, but.. :P)

Triple Response of Histamine

"At the site of injection, a reddening appears owing to dilation of small vessels, followed soon by an edematous wheal at the injection site and a red irregular flare surrounding the wheal. The flare is said to be caused by an axon reflex."

So triple response include:

- ✓ Reddens (due to vasodilation)
- ✓ Edema
- ✓ Red irregular flare (due to axon reflex)

Note: A sensation of itching may accompany these effects.

This is caused by 3 types of cells

- ✓ Smooth muscle in the microcirculation
- ✓ Capillary or venular endothelium
- ✓ Sensory nerve endings.

Note: These effects mainly involve H1 receptor activation. H2 and H3 receptors may also be involved.

Note: The injection is intradermal.

Pharmacological uses

-Nothing.
Despite that in the past they tend to use histamine to diagnose asthma patients, as they are more sensitive to histamine, if the patient has asthma he will have strong attack as soon as you give him histamine injection. But now this does not make sense as there are many safer methods to diagnose asthma.

Adverse effects

Flushing, hypotension, tachycardia, headache, wheals نفخة,
bronchoconstriction and GIT upset.

Note: These effects are observed after ingestion of spoiled fish. Histamine is produced by bacteria acting on the flesh of fish.

End of text :3
However I'm going to record some of the advices that the doctor said in the lecture/section 2 as I see them important and fun, for non-Arab he said in a way or another: BE A GOOD STUDENT.

نصائح من كلام الدكتور، بتصرُّف أدبيّ طفيف للغاية ^__^

مما يُروى عن حُجّة الأطباء الدكتور يعقوب ارشيد أنه بينما كان يخطِبُ في جمعٍ من تلاميذِ دارِ التطبيب، قال : "اعلموا أنكم إذمّا أخذتم الشهادة سيأتيكم جمعٌ يبغي أن يروّجَ لكم ترياقاً ما ،فإذا كانوا فاعلين دعوكُم إلى عشاءٍ فارهٍ يملأ بطون جياعكم و أهدوا إليكم من السمّاعات التطبيبيّة ما يعجبكم –بيدَ أنّها صَدِئة و لكن لا تبصرون- و سيدَّعون أنه ترياقٌ محدَثٌ جديد خالٍ من أيّةِ أعراض جانبيةٍ خبيثة ، فإذا ما ادّعى أحدهم هذا فاعلموا : أنّه كذّااب –و صرخَ بها صرخةً جَهور، حتى شابت الولدان و قفزت القلوب من أقفاصها :P- و تابع، إنْ كان الترياق (الدواءُ) جديداً فإنّ معرفتنا عنه شحيحة فكيف لهم أن يزعموا أنهم يعلمون خلوه من الأعراض الجانبية ، اعلموا –أبنائي، أنّ هناك من الأدوية ما يُجتثُ من سوقه بعد رواجه لأعوامَ طويلة بسبب عرضٍ جانبيٍّ له طرأ اكتشافه، فالسنون هي وحدها ما يُحكم معرفتنا عن الأدوية و يجعلنا نَمِيْزُ خبيثها من طيّبها و نحيطُ بها علماً. لذا عليكم أن تدرسوا العلوم دراسةَ مُمحّص، فإذا غامَرْتَ في شَرَفٍ مَرُومٍ، فَلا تَقنَعْ بما دونَ النّجومِ.
وستقولون: آفةُ العلم النسيان، هذا سديد، وأنا أنسى مثلكم، لكنّكم إذا ما أحسنتَم التدبير في أمور الذاكرة فلن تنسوا ما لا ينبغي نسيانه، وسيكونُ كلٌّ منكم حصيفاً. و التذكّرُ مهم؛ فإذا قالَ الجميع: نسينا نسينا، وجبَ أن نرجِع في كلِّ مرة إلى ابن سينا، و هكذا لن تُبنى العلوم.
أمّا لُهاثك وراء العلامة كالأبله، فاتركه يا مغبون، و اسعَ في العلم البهيّ تَرِبتْ يداك..