Histamine & antihistamine drugs

All of the lecture's details are included, even the intro.

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Respiratory module

JORDAN 2024/2025

Objectives

- What is histamine?
- Histamine releasers
- Clinical symptoms associated with histamine release
- Histamine receptors and its pharmacological actions
- Drugs antagonizing histamine actions
- What are meant by antihistamines?
- Clinical uses of antihistaminics
- Adverse effects of antihistaminics
- Classes of antihistaminics

موضوع الأسئلة

Histamine an inflammatory mediator

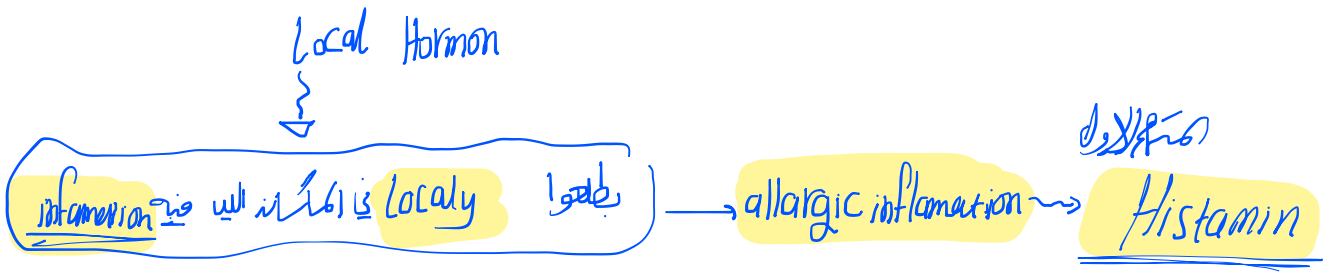
- **Histamine is an endogenous substance** (there isn't any synthesized drug called histamine) **synthesized, stored and released in** our bodies from:

(a) mast cells, which are abundant in the skin, GI, and the respiratory tract secrete largest amounts of histamine

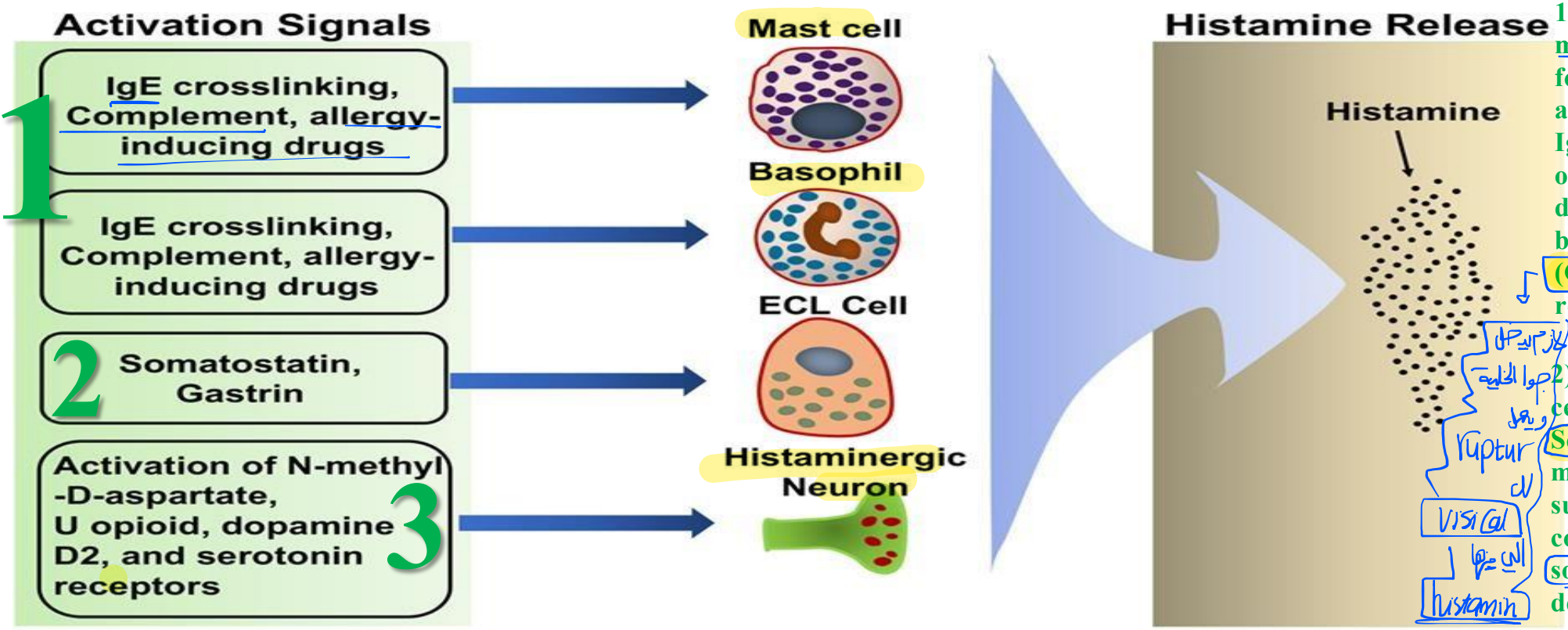
(b) basophils in the blood

(c) some neurons in the CNS and peripheral NS

Histamine is an autacoid just like eicosanoids; produced and act locally near the site of its release upon certain triggers like inflammation in allergies→ I need drugs to treat it by antagonizing histamine.



Major Histamine-producing Cells



In allergies, histamine can be released by:

1) Antigen (Ag) [Ex. food, cold, dust mite …] → binds antibody (Ab) → forming Ag- Ab complex leading to a reaction (rxn) producing IgE → IgE binds receptors on the surface of mast cells or basophils → degranulation of mast cells or basophils by the action of Calcium (Ca 2+). [IgE- mediated (dependent) release, immunological release].

2) Enterochromaffin- like (ECL) cells in GIT produce histamine and Serotonin (5HT) by similar mechanism but due to the action of substances that raises the HCl concentration like gastrin and somatostatin rather than the IgE-dependent release. [Chemical release, non-immunological, non-IgE- dependent release, non- allergic release, no Ag- Ab rxns].

Minor Histamine-producing Cells

3) Other chemical release ways include acting on its own receptors on neurons (histaminergic nerve endings):

- Morphine: Mu (μ) opioid receptors
- Serotonin: 5HT-3 receptors.
- Hallucinogens like cannabis: lambda receptor.

That being said: drugs can release histamine by either:

1) Immunological release (IgE mediated) in allergies: penicillin or non- human insulin bovine [cows] or porcine [pigs→ even if it's the closest to human ones].
2) Chemical release: morphine, cannabis … through acting on their receptors.

Histamine Release

morphin → histaminergic nerve ending

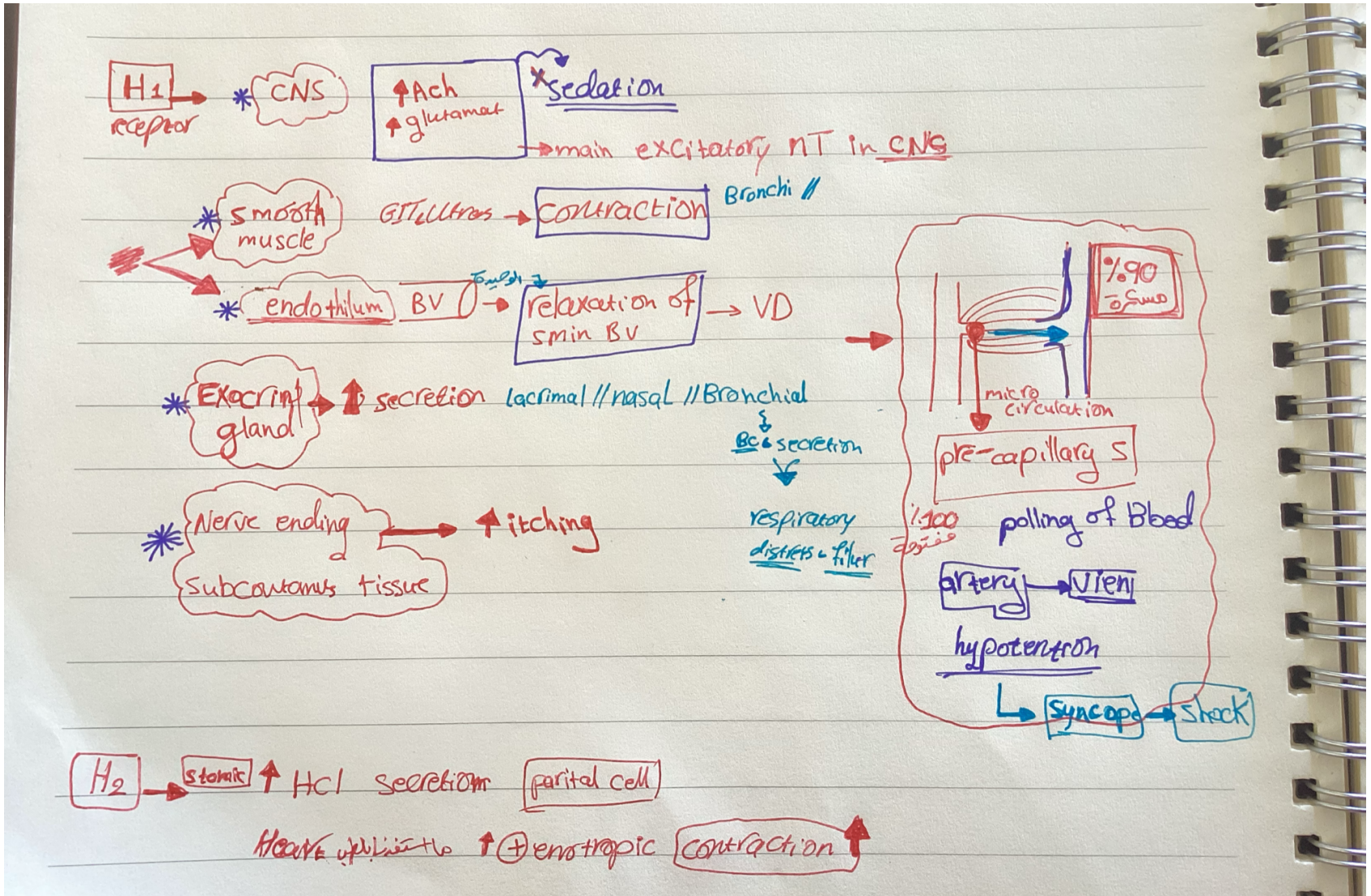
pincillin → تحسس → immunological releases

- **Immunologic Release (Cell destruction) (IgE- mediated):**
  - mast cell & basophils are degranulated when exposed to the appropriate antigen (bacterial toxins, venom, cold, food, some drugs)

- **Chemical Release (non- immunological)** : by drugs: like morphine, vancomycin & curare neuromuscular blocker, X-ray contrast media may lead to fatal anaphylactic shock; dyes used in X- ray must be tested before it's administered.

X-ray → الأشعة

مسألة من الصيدلة اللي بتنحط قبل صورة الأشعة


H1 receptor
CNS
↑Ach
↑glutamat
sedation
main excitatory NT in CNS
smooth muscle
GIT, Uterus
contraction
Bronchi //
endothilum
BV
relaxation of smin BV
VD
Exocrin gland
↑ secretion
lacrimal // nasal // Bronchial
Bc ↑ secretion
respiratory distress ↑ filter
Nerve ending
↑itching
subcontanus tissue
%90
micro circulation
pre-capillary S
%100
pooling of blood
artery
vien
hypotention
syncope
shock
H2
stomic
↑ HCl secretion
parital cell
Heart
↑ (+) enotropic contraction

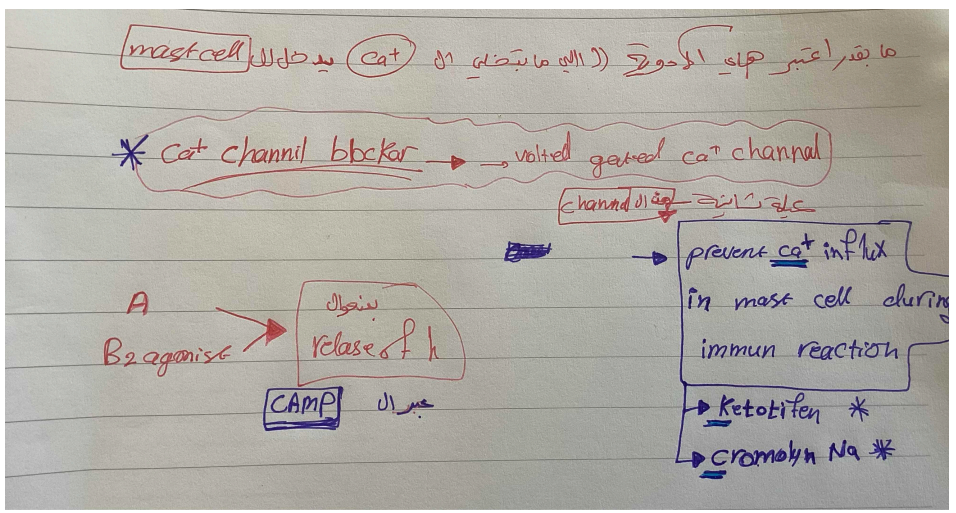
H3 → PNS // CNS

⊖ feedback of histamin

realeas of بتحكم

neurotransmettar من → Histamin

H4 → immun cell ↑↓ imunty



Clinical Symptoms Associated With Histamine Release

- **Amount released- related side effects:**

Little •mild/cutaneous

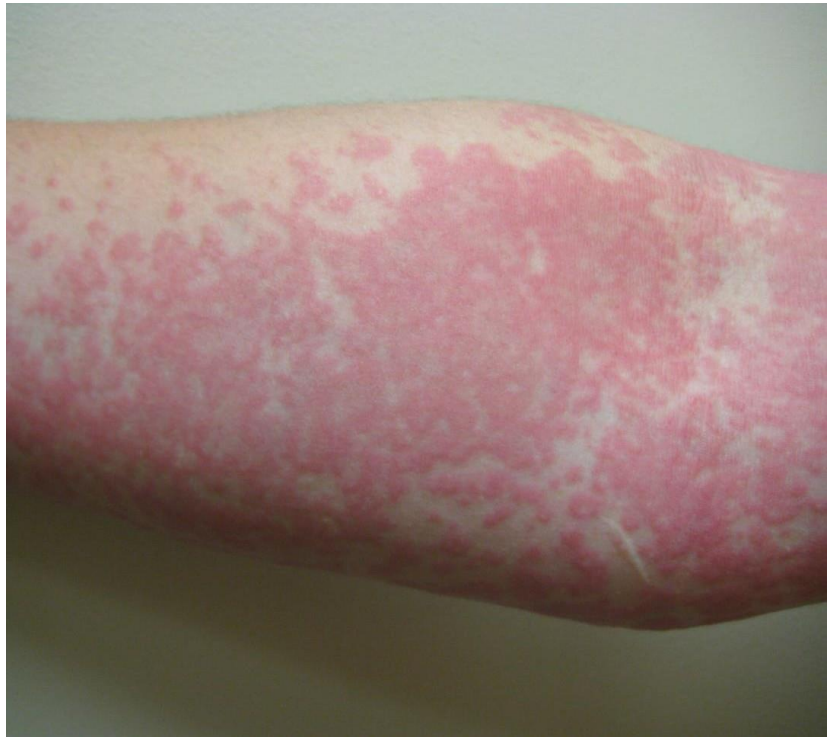
- **Skin reactions:** erythema **(redness)**, urticaria **(hives)**, and/or itching

Moderate •mild to moderate

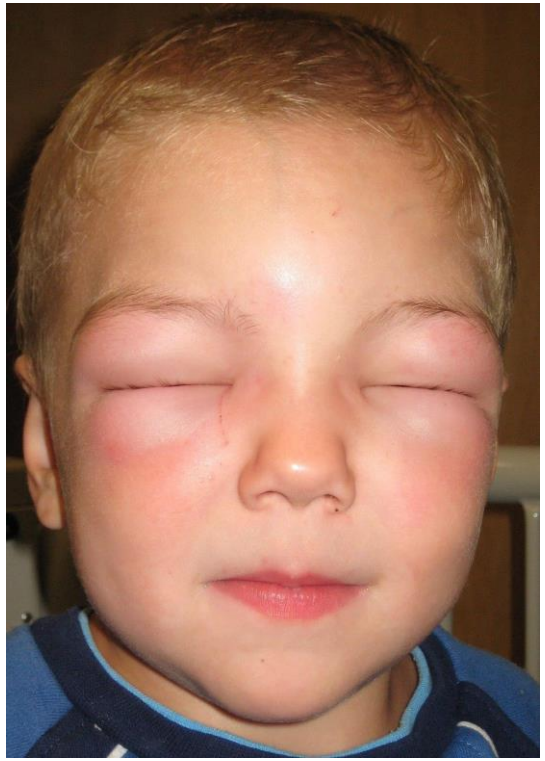
- **1)** skin reactions, **2) cardiac rxns:** tachycardia, dysrhythmias, moderate hypotension, **3) respiratory rxns:** mild respiratory distress **(manifested as bronchospasm) → still under control**

Massive •severe/anaphylactic

- severe hypotension **followed by syncope and shock,** ventricular fibrillations, cardiac arrest, bronchospasm, respiratory arrest **as a result of anaphylactic shock**



Urticaria (Hives)
Honeycomb like appearance



Angioedema
Severe VD and increased permeability

Histamine Receptors: Distribution and Function (this is the original slide, details are split in the next two slides)

- Histamine has four histamine H_1, H_2, H_3, & H_4 G-protein coupled receptors:

- H1 – **Smooth muscle fibers, endothelium, CNS, nerve endings:**
- Bronchoconstriction, vasodilation (relaxation of precapillary sphincters), motion sick, memory and wakefulness, increasing secretions of exocrine glands, sever itching

- H2 – **gastric parietal cell, heart, mast cell**:
- Regulate gastric acid secretion, positive inotropic, inhibition of IgE-dependent degranulation (negative feedback).

- H3 - **CNS cells, and some in peripheral NS. Presynaptic**:
- feedback inhibition of histamine synthesis and release. They also control release of DA, GABA, ACh, 5-HT & NE

- H4 - **Highly expressed in immune cells**: immunity modulation

Histamine Receptors: Distribution and Function

- Histamine has four histamine H_1, H_2, H_3, & H_4 G-protein coupled receptors:
  - H1 – Found in: **Smooth muscle fibers** (found in bronchi, BVs and exocrine glands. Histamine always causes VC except [1st exception] in BVs' endothelium → VD. Why the controversy? Because they stimulate different second messengers → different actions), **endothelium, CNS** (histamine increases the release of Ach and glutamate; the latter is the main excitatory neurotransmitter in CNS producing alertness and stimulated memory. Antihistaminic drugs → drowsiness , **nerve endings** (subcutaneous sensory neurons → itching):
  - Causing: Bronchoconstriction (bronchospasm → respiratory failure), vasodilation (relaxation of precapillary sphincters these sphincters control the blood going from arteries to veins. Normally, 90% of them are closed and only 10% are open but upon histamine stimulation, 100% of them will open causing → pooling of blood from arteries to veins → hypotension → syncope → shock), treating motion sick (NV when in circular motion; it's caused due to endolymph movements in all directions → sending lots of signals to cerebellum through vestibulocerebellar pathway → no balance. We treat it with either histamine blockers or muscarinic blockers like scopolamine and atropine), memory and wakefulness, increasing secretions of exocrine glands (lacrimal → tears, nasal → discharges and bronchial → secretions), sever itching.

Histamine Receptors: Distribution and Function

- Histamine has four histamine H_1, H_2, H_3, & H_4 G-protein coupled receptors:

- H2 – **gastric parietal cell, heart, mast cell**:
- Regulate gastric acid secretion **(GIT module, H2 blockers are used for peptic ulcer)**, positive inotropic **(increases contractility, of no clinical application)**, inhibition of IgE-dependent degranulation **(of no clinical application)** (negative feedback).

- H3 - **CNS cells, and some in peripheral NS. Presynaptic**:
- feedback inhibition of histamine synthesis and release. They also control release of **many neurotransmitters like:** DA, GABA, ACh, 5-HT & NE. **These drugs are still underdevelopment and no released to the market.**

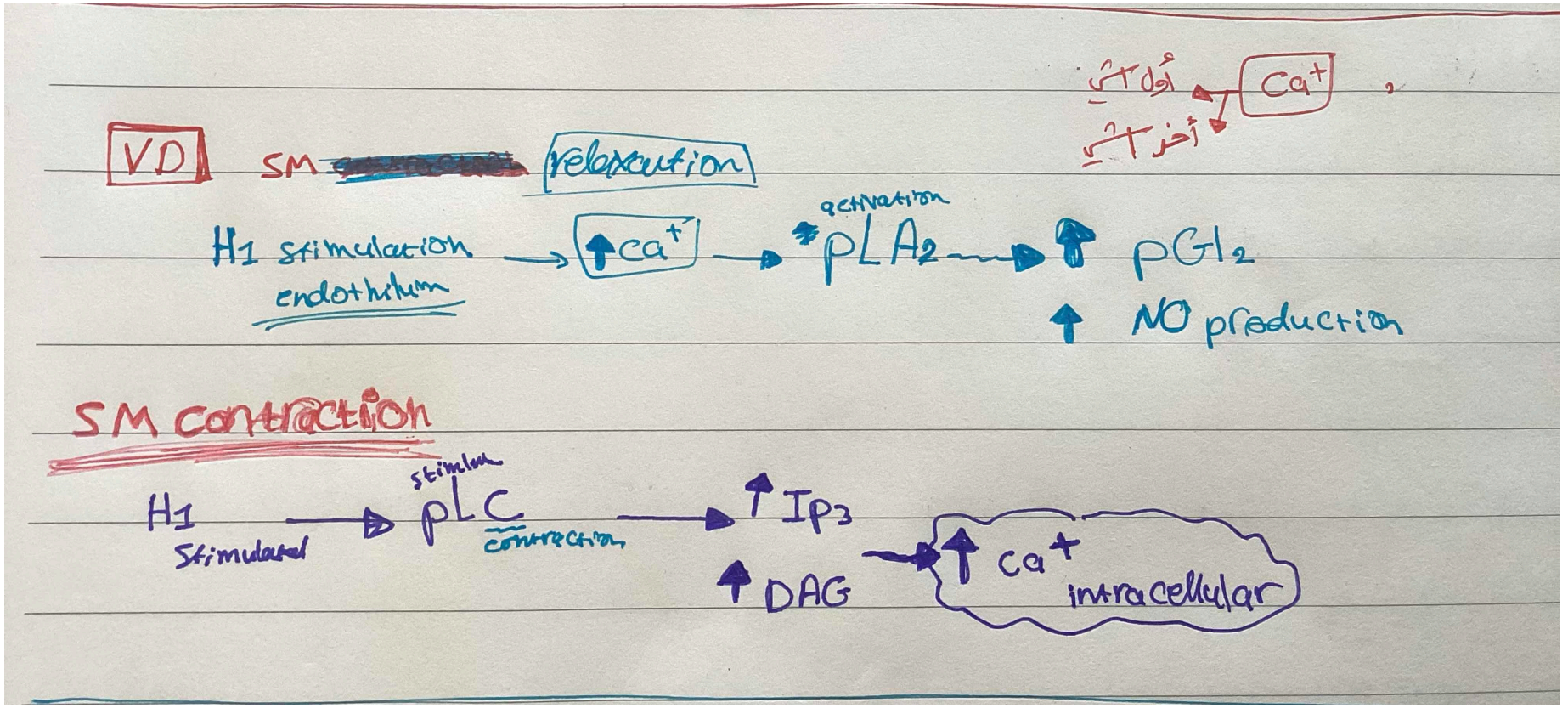
- H4 - **Highly expressed in immune cells**: immunity modulation. **These drugs are still underdevelopment and no released to the market.**

Molecular biology of H1 receptors

❑ **Vasodilatation** is via endothelial H_1 receptors

•H_1 stimulation → Increased intracellular Ca^{2+} → Activation of PLA_2 → PGI_2 & NO production → Diffusion to smooth muscles → vasodilatation if calcium was the initial step → VD

❑ **Contraction of bronchi, intestine and other smooth muscle fibers** occur via stimulation of *PLC* *phospholipase C*-*coupled* H_1 *receptors* followed by increased IP_3 inositol triphosphate & DAG diacylglycerol: increasing intracellular Ca^{2+} if calcium was the last step → VC

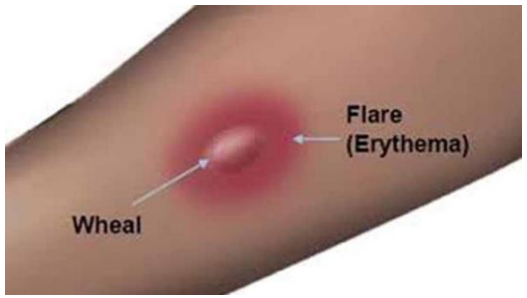

VD
SM
relaxation
H1 stimulation
endothelium
ca+
activation
pLA2
pGI2
NO production
SM contraction
H1
Stimulated
stimulus
pLC
contraction
IP3
DAG
Ca+
intracellular

Triple Response of Willis

Subdermal (subcutaneous, SQ) histamine injection causes:

1. 1st manifestation Red spot (few mm in size) in seconds: direct vasodilation effect, H1 receptor mediated
2. after a while, Flare (1cm beyond site of injection → outside the center): axonal reflexes (irritation to sensory subcutaneous nerves → itching), indirect vasodilation, and itching, H1 receptor mediated
3. lastly, Wheal of elevated surface (1-2 min) same area as original spot, edema due to increased capillary permeability, H1 receptor mediated

The three of them combined will give the honeycomb appearance of urticaria (hives).



Drugs antagonizing histamine actions

- 1- Physiologic antagonism? When two drugs act on same target but at different receptors producing antagonizing effects: Ex. Histamine on H1 receptor and adrenaline on alpha 1 receptor (the life saving in anaphylactic shock). I may also give anti- histamine and CS.
- 2- Mast Cell Stabilizers they decrease Ca 2+ influx → no Ca 2+ entry to mast cells → no mast cells degranulation. Only two drugs are in this class: (Cromolyn Na sodium, ketotifen) NOT to be confused with the known calcium channel blockers (CCBs) for hypertension
- 3- Receptor antagonism:
- H1 Receptor Antagonists (1st and 2nd generation)
- H2 Receptor Antagonists (Ranitidine, Cimetidine) well- used for peptic ulcer cases.
- H3 Receptor Agonist and Antagonists (potential new drugs being developed)
- 4- Immunotherapy (desensitization), it happens in either of 2 ways:

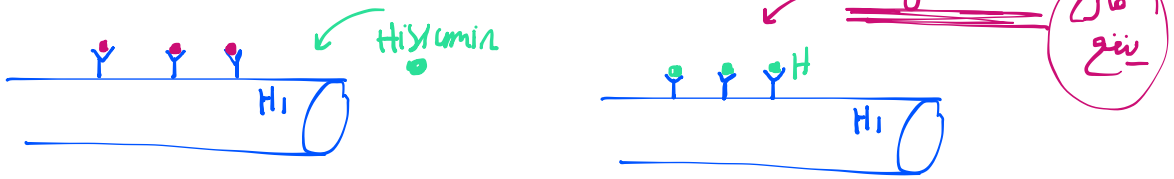
A) If the allergen is known: Ex. Egg, gradual exposure by giving doses of eggs' Ag produced by big pharma → tolerance to this Ag (it explains why most people have their childhood allergies disappeared at later ages of life).

B) If the allergen is unknown: a prepared kit of different allergens will be tested on the forearm, one rxn happen to any of them it's now known and we can carry on the same procedure in A.

What is an antihistaminic?

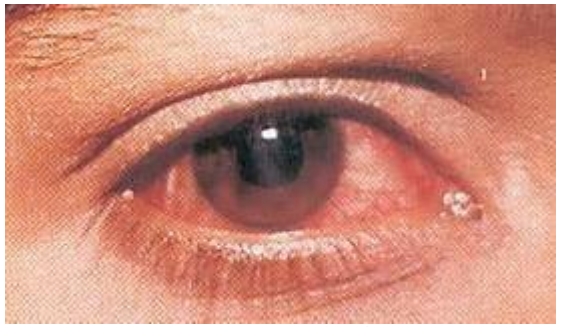
Contrary to the common belief, when we say antihistaminic we only refer to H1 blockers not the H1, H2, H3 and H4 blockers altogether.
(this is the original slide, details are split in the next two slides)

- A drug that reduces or eliminates the effects mediated by histamine
- The term antihistamine **only refers to H_1 receptor antagonists**
- Antihistamines compete with histamine for binding sites at the receptors
  competitive antagonists.
- Antihistamine cannot remove the histamine if it is already bound
- More effective in preventing the actions of histamine rather than reversing them (It prevent its release but once histamine is released it can't be removed; that's why it:
- Should be given early in treatment, before massive amounts of histamine are released and all the histamine binds to the receptors



Clinical Uses of Antihistamines

(this is the original slide, details are split in the next two slides)



- **1- Allergy**: (both 1st and 2nd generations)
- Allergic rhinitis (common cold)
- Allergic conjunctivitis (pink eye)
- Anaphylactic reactions (severe allergies)
- Allergic dermatological conditions:
- A- Urticaria (hives)
- B- Angioedema (swelling of the skin)
- C- Pruritus (atopic dermatitis, insect bites)
- **2- Motion sickness, vertigo** (first generation H_1-antihistamines)
- **3- Sedative/sleep aid** (1st generation)
- 4- **Carcinoid syndrome**: cyproheptadine

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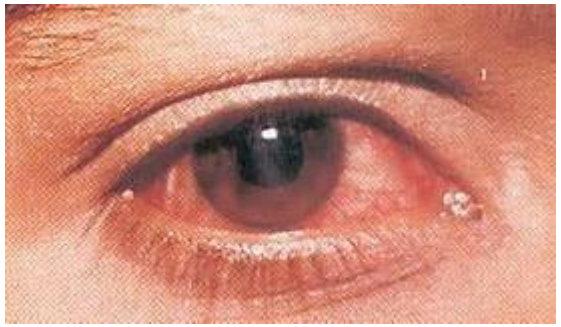


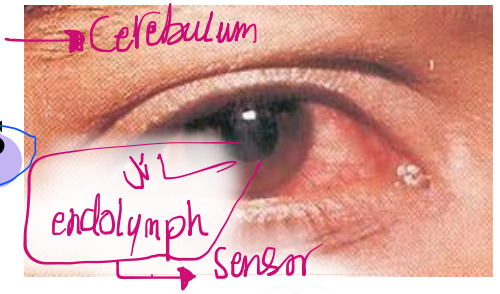
We can say that H1 and H2 blockers can be used in almost all allergic conditions except [2nd exception] bronchial asthma; as there are roughly 30- 40 receptors other than histamine (histamine isn't the main one) → it would be of a very little -if any- medical use but it will definitely cause side effects.

Bronchoconstriction

Sedation

Clinical Uses of Antihistamines

- **2- Motion sickness** except [3rd exception] Ménière's disease because it has different pathophysiology, **vertigo** by blocking both M1 and H1 receptors. (first generation H_1-antihistamines because it's the only generation capable of crossing blood brain barrier (BBB) fully to reach the cerebellum)
- **3- Sedative/sleep aid** (1st generation) The only one capable of crossing BBB to cerebellum.
- **4- Carcinoid syndrome** (carcinoid tumors are cancers of ECL (produces histamine and serotonin, locally malignant, and can only metastasize within its original sites (liver, pancreas or intestines but never far away). As it causes increase in serotonin → flushing and diarrhea (carcinoid syndrome). There is only one drug useful from antihistaminic for this case which is: cyproheptadine (Both 5HT-3 and H1 receptor blocker).



Adverse effects

- **Associated with the first generation H_1-antihistamines and due to their lack of selectivity for the H_1:**
- **1- Sedation:** lipophilic: pass BBB, it is contraindicated (CI) in cases where full alertness is needed: drivers, students …
- **EXCITATION** and convulsions in children under 6 years age (atropine-like)
- **2- Atropine-like action:**

Symptoms of atropine- like action can be summed in: زغلولة الناشفة حبست جوزها أبو سريع

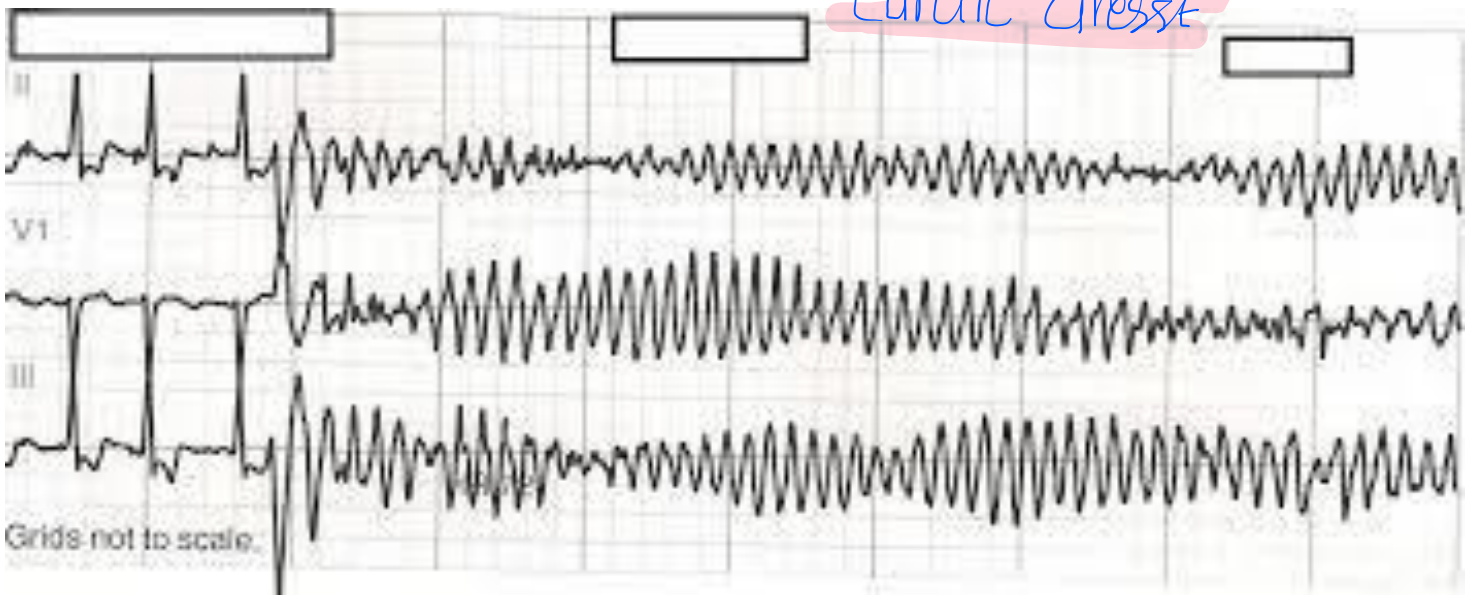
- Blurred vision زغلولة , dry mouth الناشفة , urine retention حبست(esp. old age, esp. in males due to prostate enlargement), glaucoma جوزها(old age) and tachycardia ابو سريع.
- **3- Alpha blocking action:** orthostatic hypotension (drowsiness upon standing) and tachycardia
- **4- Serotonin blocking action** (cyproheptadine): weight gain, dry mouth, drowsiness
- 5- Newer second generation H1-antihistamines are more selective for the peripheral histamine receptors and have less side effects, BUT
- **Serious types of arrhythmias(fatal)** ventricular arrhythmias: (Torsade de pointes twisting points) prolongation of QT- interval: astemizole (it blocks potassium channels in hearts). 6 sites deaths around the world where due to its use.

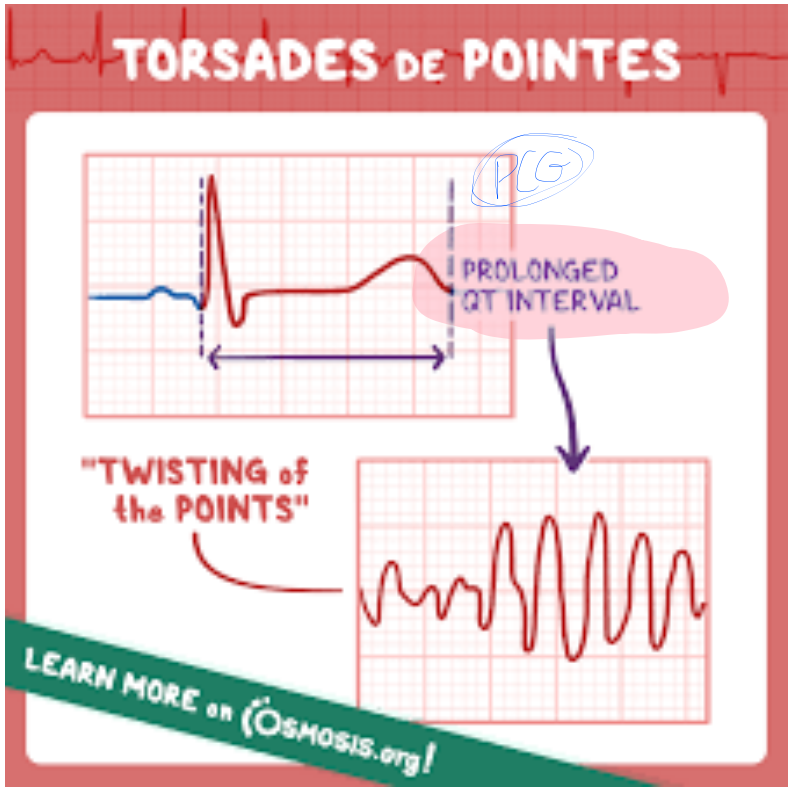
2nd → ventricul arrthmias

QT interval

↓

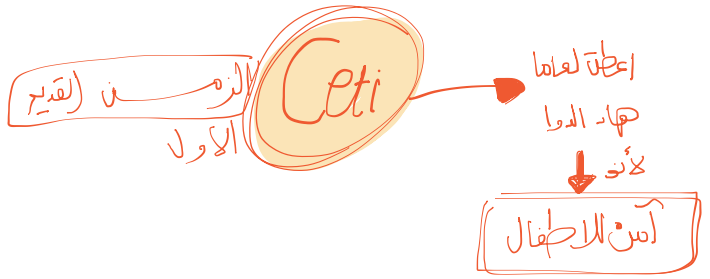
Cardic cirest





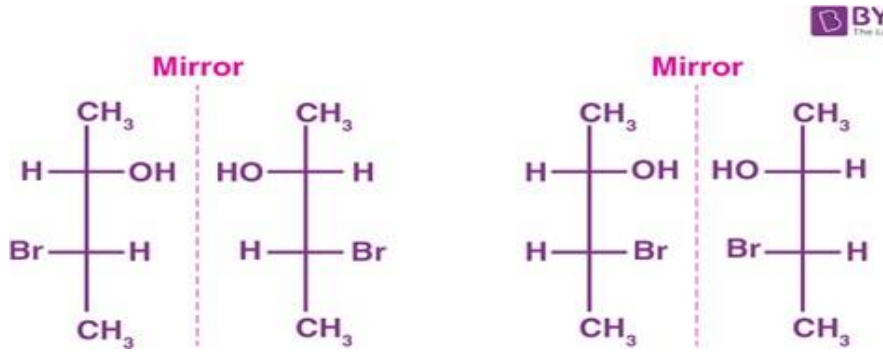
First generation H_1 receptor antagonist

- **Mepyramine**
- **Diphenhydramine:**
- Oldest
- Available over the counter
- Because it induces sedation, it's used in nonprescription sleep aids
- **Dimenhydrinate**: Anti-emetic for motion sickness
- **Cyclizine**: motion sickness
- **Cetirizine (Zyrtec):** allergies and is safe to use in children as young as 2 (because it can only cross BBB slightly → simple if any sedation. For this reason some textbooks may classify it as second generation.
- **Kitotifen** mast cell stabilizer + Cromolyn Na prevent Ca^{+} influx
- **Cyproheptadine** for carcinoid syndrome



- **Levocetirizine:**
- This drug is the active enantiomer (mirror reflection) of cetirizine better efficacy and lower side effects of Levo.
- Also it is not metabolized and is likely to be safer than other drugs due to a lack of possible drug interactions. Of higher efficacy and lower side effects.
- It ~~does not~~ slightly cross the BBB and ~~does not~~ slightly cause significant drowsiness

Sedation



Second generation H_1-receptor antagonists

- These are the newer drugs and they are much more selective for the peripheral H1-receptors involved in allergies than to the H1-receptors in the CNS
- Therefore, these drugs provide the same relief with many fewer adverse side effects
- They are less lipophilic than the first generation drugs, therefore they do not cross the BBB as readily

1st generation	2nd generations
• Short to intermediate action 2-3 times daily	• Long acting Once daily 24h
• BBB cross	• Poor penetration
• Sedative action	• No
• Produce anti muscurnic side effects	• No
• Also block auonomic receptors	• No
• Cheap	• Relatively expensive

Atropin like

Second generation H_1-receptor antagonists

- Astemizole & Terfenadine
- Have been taken off the market in most countries because of adverse interactions with erythromycin and ketoconazole (Both are microsomal enzyme inhibitors) and have effects on cardiac potassium channels
- Loratidine, desloratadine (active metabolite of Loratidine; Desloratadine is of higher potency and lower side effects.

Third generation H_1-receptor antagonists

- These drugs are derived from second generation antihistamines
- They are either the active enantiomer or metabolite of the second generation drug designed to have increased efficacy and fewer side effects
- **Fexofenadine** (the active metabolite of terfenadine, Fexofenadine is of higher potency and lower side effects.), was approved in July 1996

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الحمد لله

Thank you