Histamine L1& L2

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Histamine is a chemical messenger, an **autocoid**, that mediates a wide range of cellular response, including allergic reaction, truma, inflammatory reactions, gastric acid secretion, immune involvement and neurotransmission in brain.

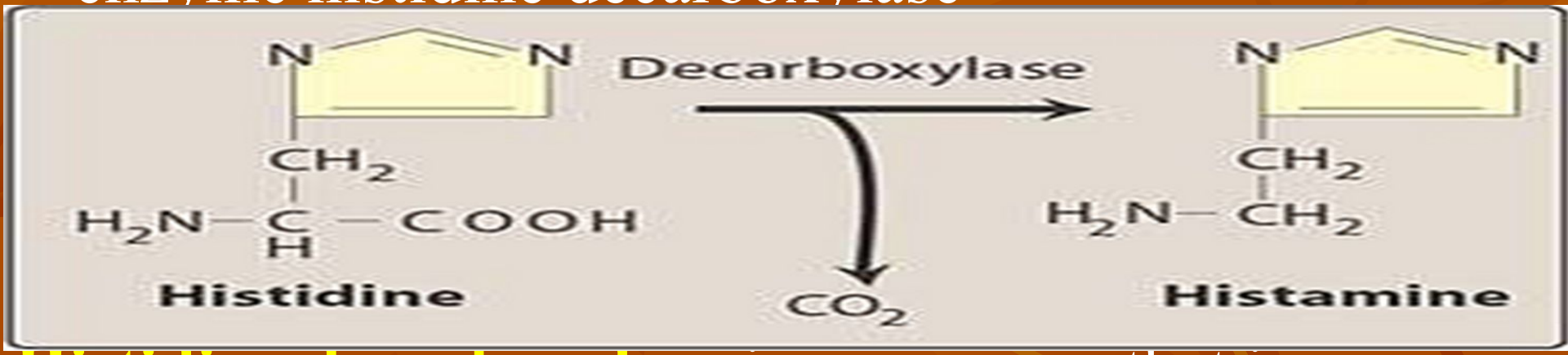
NOTE:

** Autocoid is a biological factor which act like local hormone and act near the site of synthesis.

The word "autacoid" comes from the Greek: **autos (**self**) and **akos** (**medicinal** agent)

Histamine has no clinical applications, but agents that inhibit the action of histamine (antihistamines or histamine receptor blockers) have important role .

Synthesis: Histamine is an **amine** formed from the decarboxylation of the amino acid histidine by the enzyme histidine decarboxylase



Histidine decarboxylase is an enzyme that is expressed in many cells in the body, including:

CNS neurons,

gastric parietal cells,

mast cells, and basophils.

Histamine is **present** in practically **all tissues**, with** significant amounts in the lungs, skin, blood vessels, and GIT, with high concentrations in mast cells and basophils

,**In mast cells**

histamine is stored in granules as an **inactive complex**

: composed of

Histamine

Leukotrienes

.anionic protein

Release of histamine:

The release of histamine may be the primary response to some stimuli including

1- Allergies

2- Anaphylaxis (severe allergic reaction……)

3- Cell destruction as result of

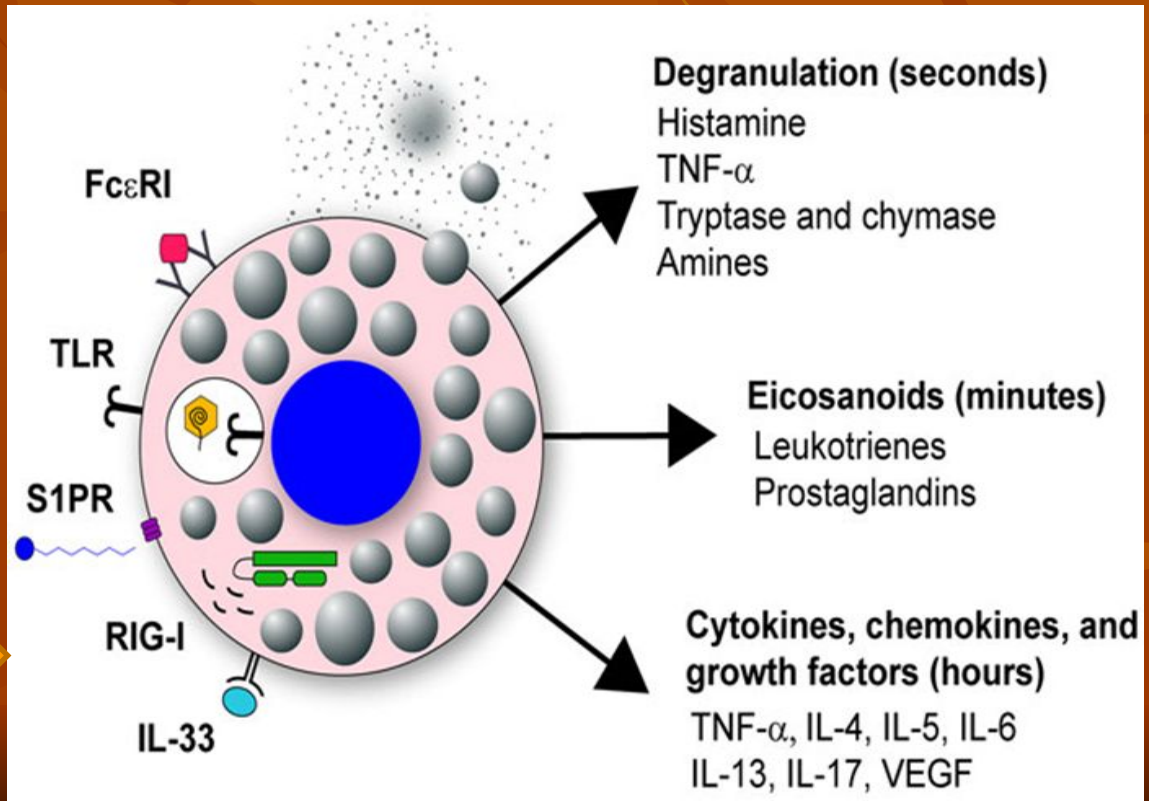
a- Cold

b- Bacterial toxins

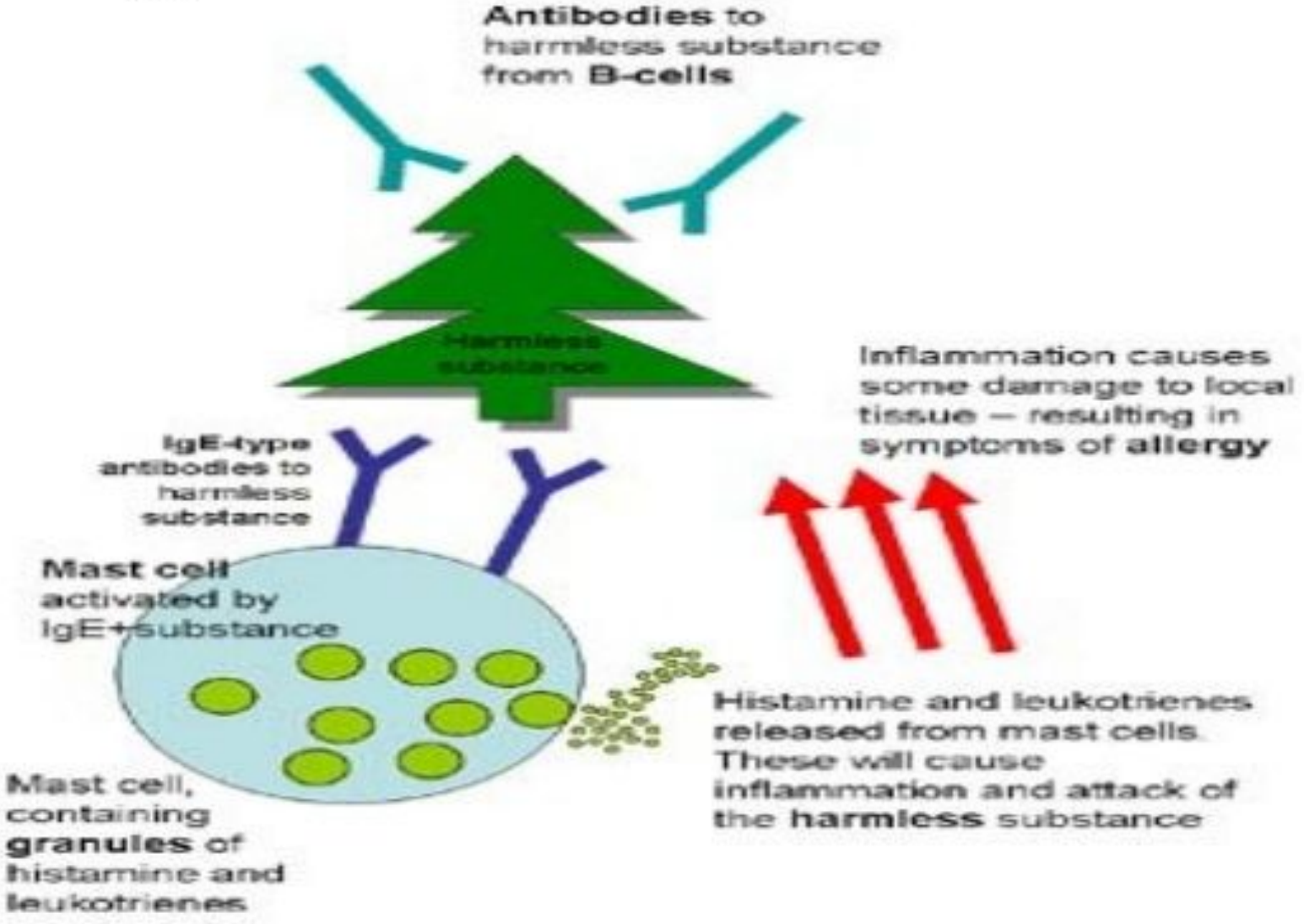
c- Bee stings or

d- Trauma.

*just information



what is the role of histamine in allergy?



If the **release** of histamine is **slow** enough to permit its **inactivation** before it enters the bloodstream, a **local** allergic reaction results

If histamine **release** is too **fast** for inactivation, a full-blown **anaphylactic** reaction occurs

.

In **most of cases**, histamine is **just one** of several .chemical mediators released

RECEPTORS

- Histamine receptors are belonging to the family of G-Protein coupled receptors.
- The sub types of histamine receptors are:
  - H_1
  - H_2
  - H_3
  - H_4

RECEPTOR	H_1	H_2	H_3	H_4
LOCATION	Brain,GIT,CVS Lymphocytes.	Myocardial cells,parietal cells	CNS,myentric plexus, gastric mucosa	Spleen,thymus ,T-cells, eosinophils.

Mechanism of histamine action:

Histamine released in response to various stimuli exerts its effects by binding to one or more of four types of histamine receptors:

H1, H2, H3 and H4 receptors.

Histamine has **no therapeutic use** but some drugs can cause histamine release like (d-tubocurarine and morphine and vancomycin) of attention.

Action of histamine:

on H1 receptors include

on exocrine secretion: it increases production of nasal and bronchial mucus resulting in respiratory distress.

on Bronchial smooth muscle: constriction of bronchioles results in symptoms of asthma and decreased lung capacity.

Intestinal smooth muscle causes

contraction results in intestinal cramps and diarrhea.

Sensory nerve ending, causes

itching and pain.

On H1 and H2 receptors

On cardiovascular system :

it **lowers** systemic **blood pressure** by reducing peripheral resistance, this means **hypotension** may occurs, Causes positive **chronotropism** (i.e increases heart rate) (mediated by H2 receptor) and a positive **inotropism** (i.e: increases contractility) (mediated by both H1 and H2 R) .

*Histamine promotes **vasodilation** of small blood vessels by causing the vascular endothelium to release **nitric oxide**.

On skin : (H1 receptor and less H2 receptor)

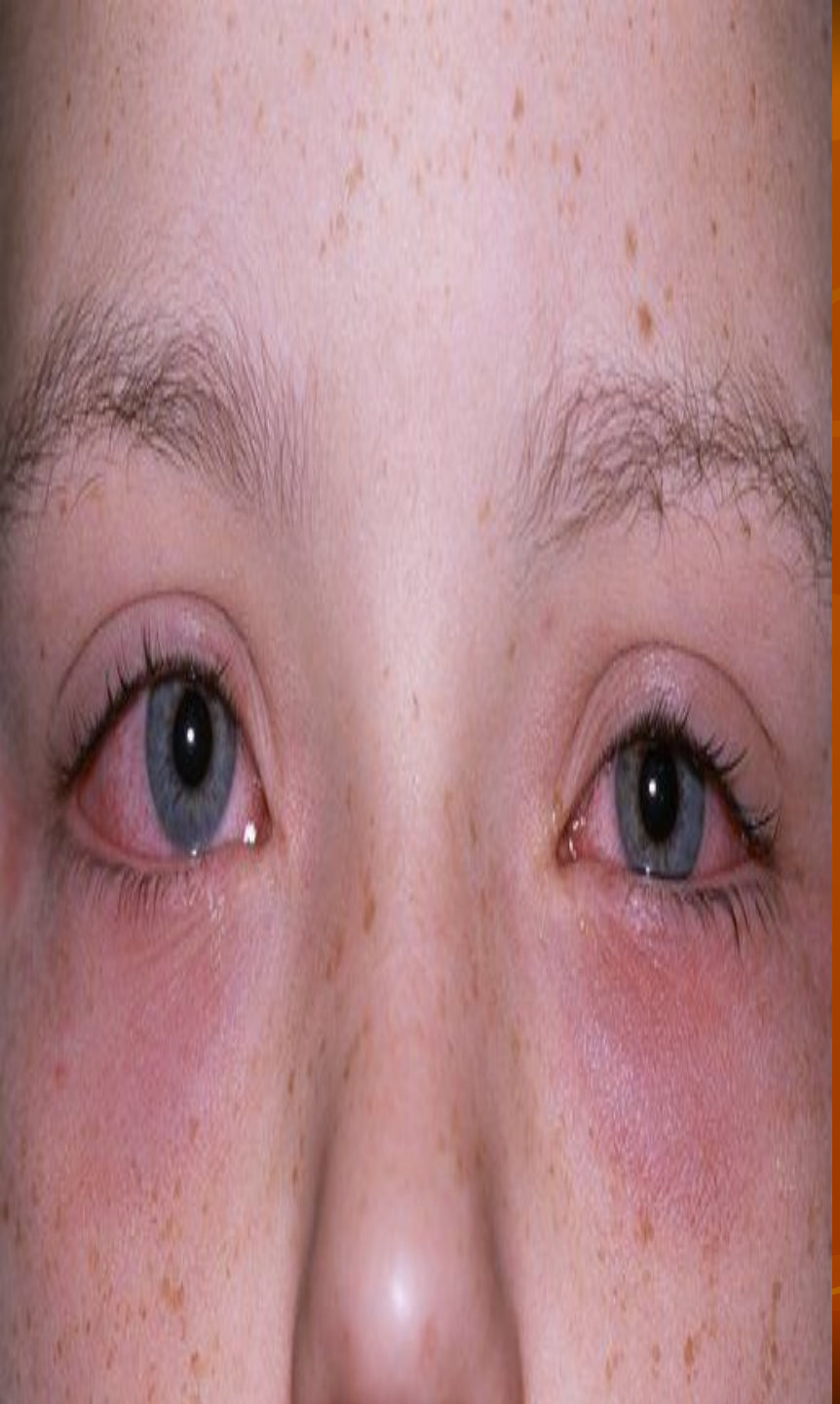
causes the classic **" triple response“** phenomenon which characterized by

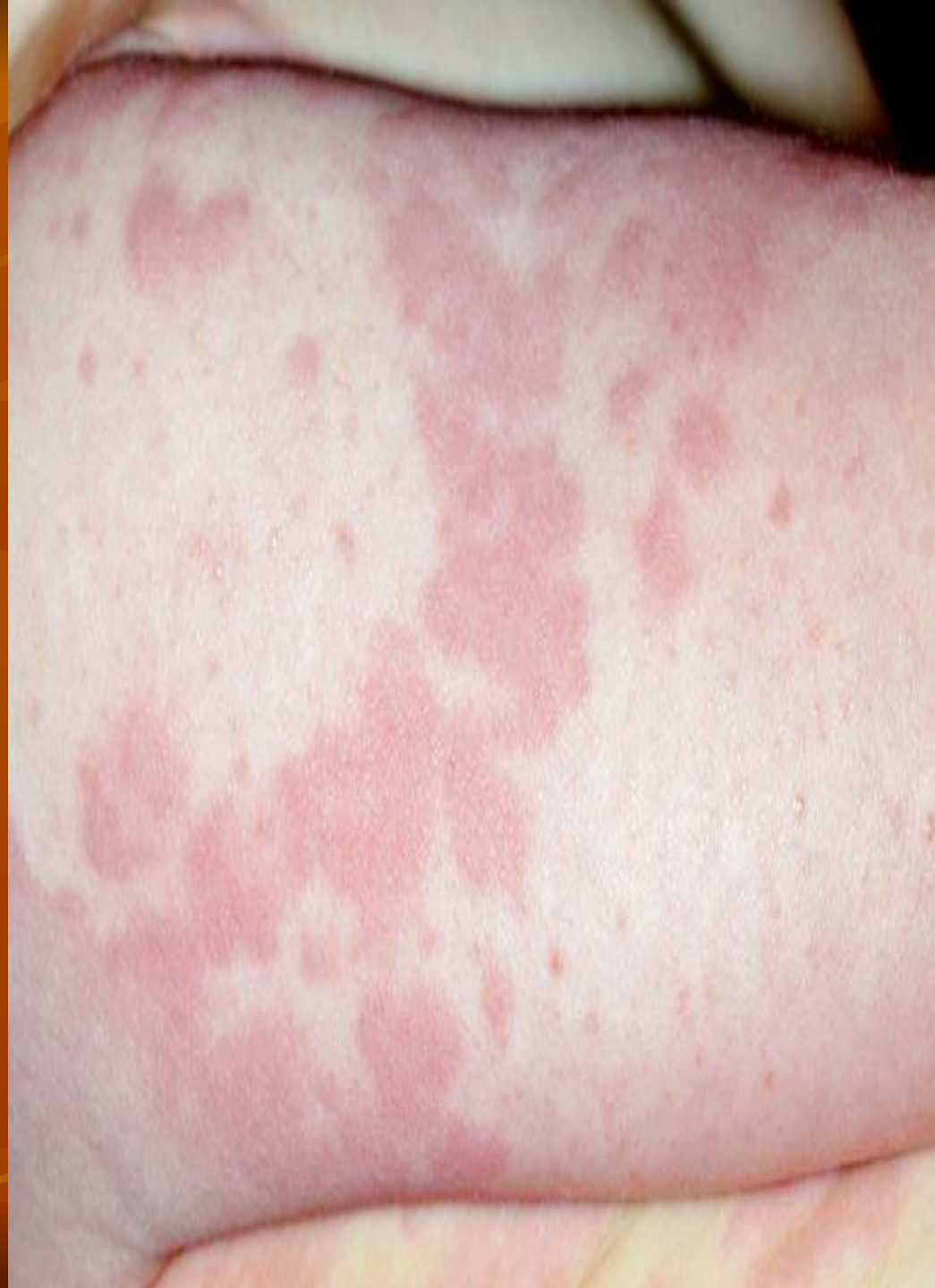
1- **Flush** (**reddening**) due to dilatation of blood vessels.

2- **Wheal formation** (edema) due to increase permeability of the capillaries results in leakage of proteins and fluid into the tissues.

3- Flare (due to axonal reflex).

If the effect is severe it cause peripheral nerve involvement resulting in itching and pain





Thus Histamine H1 receptors **mediate** many **pathological processes**, including allergic rhinitis, atopic dermatitis, conjunctivitis, urticaria, bronchoconstriction, asthma, and anaphylaxis.

On H2 receptors

On stomach:

Causes stimulation of gastric acid secretion.

Histamine H3 receptors act as presynaptic **autoreceptors** that **inhibit** the synthesis and release of histamine in the **histaminergic** neurones in the central nervous system (**CNS**)

They also act as **hetero-receptors** on nonhistaminergic neurones, modulating the release of other neurotransmitters such as 5-hydroxytryptamine, dopamine, acetylcholine, noradrenaline and GABA in the **CNS and periphery.**

The H4 receptor

is **expressed** in various cells of the **immune system** and mast cells.

It induces the **chemotaxis** of eosinophils and mast cells.

It has also been identified on **lymphocyte T** cells and **basophils**..

Antihistamines:

The effects of histamine can be **opposed** in three ways:

1-Physiological antagonist: by using a drug that act on **other** type of receptor , not on histamine receptor, and act with opposite effects of histamine

e.g. **epinephrine.**

2-Pharmacological antagonist: by blocking histamine **binding** to its site of action(**receptors**) e.g. using **competitive** H1- and H2- receptor antagonists.

e.g Cimetidine. Doxylamine

3-Stabilizing wall of mast cell : by preventing the release of histamine from storage cells; **glucocorticoids, sodium cromoglicate and β2-agonists** can **suppress IgE - induced release** from mast cells.

The H1 receptor blockers can be divided into First, second and third generation drugs.

First-generation H1 blockers drugs are

1- **widely** used

2- they are **effective**

3- inexpensive

4- penetrate the CNS and cause **sedation**.

5- they are **non specific**, thus tend to **interact** with other receptors producing a variety of unwanted **adverse effects**.

6- it divided according to sedative property into:

a- **Highly sedative:** Diphenhydramine, Dimenhydrinate, Promethazine, Hydroxyzine., etc

b- **Moderatly sedative** Pheniramine, Cyproheptidine, Meclizine, Cinnarizine etc.

c- **Mild sedative:** Chlorpheniramine, Dexchlorpheniramine, Dimethindene, Triprolidine, Cyclizine, Clemastine etc.

In contrast

Second-generation agents are

1- **Specific** for H1 receptors,

2- Do **not penetrate** the **blood-brain barrier** .

3- They show **less CNS toxicity** than the first-generation drugs.

4- **Less** or **Not** cause **sedation**

Among the second-generation agents, desloratadine, fexofenadine , and loratadine show the least sedation.

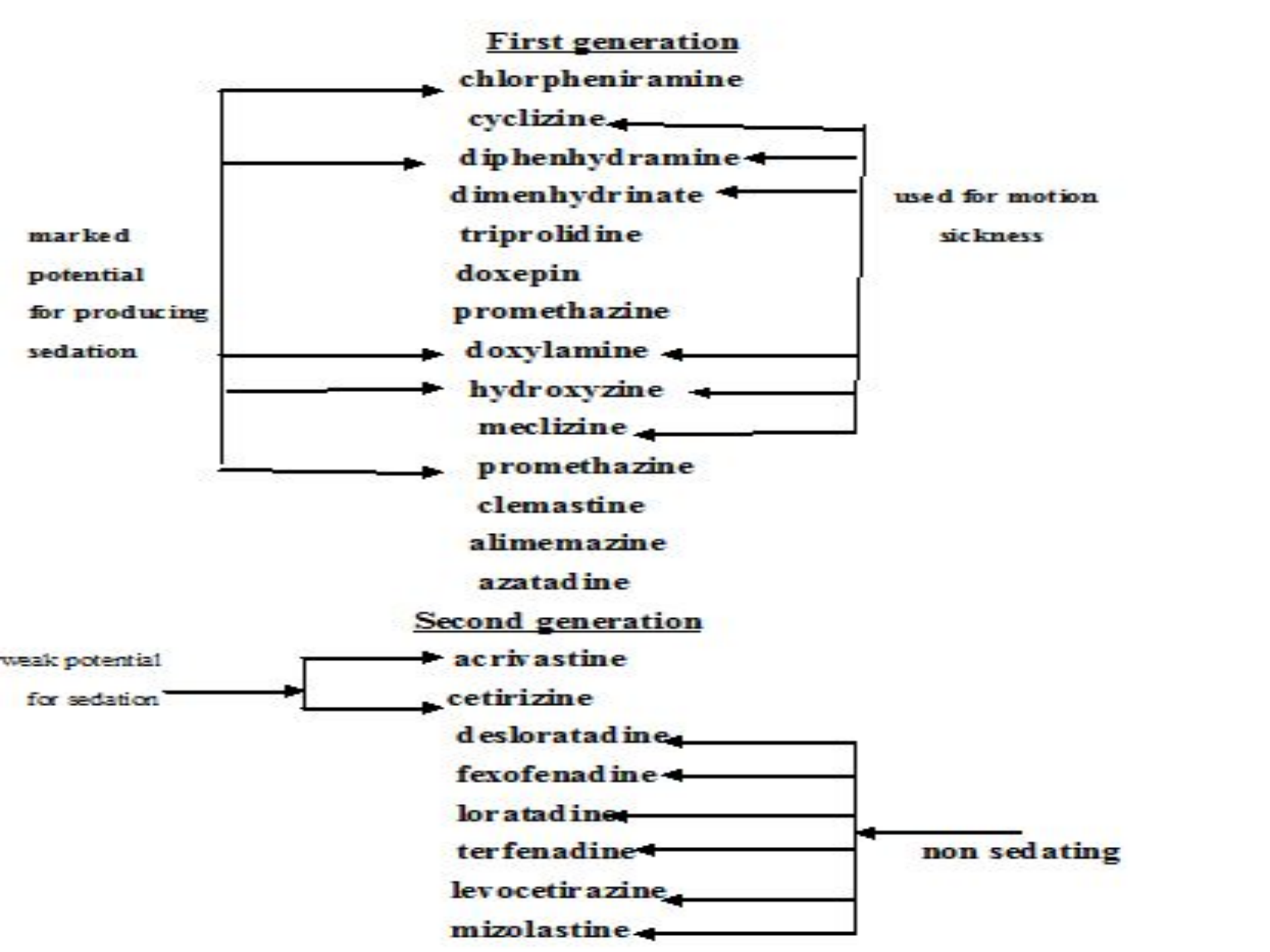
Cetirizine and levocetirizine are partially sedating.

****Generally**, all generations have **longer duration** of action permit **single daily** dose.

Third generation H1 blockers(some time separated from 2nd generation) : 2 drug

LORATIDINE and ACRIVASTINE

These have increased efficacy with fewer .adverse drug reactions


First generation
chlorpheniramine
cyclizine
diphenhydramine
dimenhydrinate
triprolidine
doxepin
promethazine
doxylamine
hydroxyzine
meclizine
promethazine
clemastine
alimemazine
azatadine
used for motion sickness
marked potential for producing sedation
Second generation
acrivastine
cetirizine
desloratadine
fexofenadine
loratadine
terfenadine
levocetirazine
mizolastine
non sedating
weak potential for sedation


MEMBER'S MARK
Cetirizine
Hydrochloride Tablets, 10mg/Antihistamine
Allergy
Cetirizine


Loratadine
10 mg Tablets
10 mg
Telfast 120 mg film-coated tablets
fexofenadine hydrochloride
Oral use
30 film-coated tablets
SANOFI


ZYRTEC
Allegra Allergy
24 hour
33% MORE FREE!
Non-Drowsy
Claritin
24 hour
Indoor & Outdoor Allergies
40


Non-Drowsy
Claritin
loratadine tablets 10 mg
antihistamine
24 hour
Indoor & Outdoor Allergies
Claritin
100
100 TABLETS

Pharmacokinetics: they are

1-**Well absorbed** orally.

2- **High bioavailability**

3- **Distributed** in **all tissues**, including the CNS.

4- **All** first-generation H1 antihistamines and **some** second and third generation H1 antihistamines such as loratadine and desloratadine are **metabolized** by the hepatic **cytochrome P450 system.**

6- Levocetirizine is the active metabilite of cetirizine

7-**Cetirizine and levocetirizine** is excreted largely unchanged in the **urine** and

fexofenadine is excreted largely unchanged in the **feces**.

8- **Tolerance not occur**

9- **Azelastine and ketotifen also have mast cell–stabilizing.**

Note: This slide for your informations:

10- After a single oral dose, the onset of action 1 to 3 hrs

11-The average half-life is 4 to 6 hours, except for that of meclizine and the second-generation agents, which is 12 to 24 hours, allowing for once-daily dosing.

12- Maximum serum levels occurring at 1 to 2 hours

13- Azelastine, olopatadine, ketotifen, alcaftadine, bepotastine and emedastine are available in ophthalmic formulations that allow for more targeted tissue delivery.

Azelastine and olopatadine have intranasal formulations.

Therapeutic uses:

1- Allergic and inflammatory conditions, like allergic cough, conjunctivitis and reactions to insect bites or stings……..

especially those are caused by antigens acting on **IgE** antibody-sensitized mast cells. However, the H1 receptors blockers are **ineffective** in treating bronchial asthma, because histamine is just one of several mediators of that condition and glucocorticoids show greater anti-inflammatory effects than H1 antihistamines in such case.

Antihistamines are **most effective** when used **prophylactically** before allergen exposure rather than as needed.

2- Motion sickness and nausea

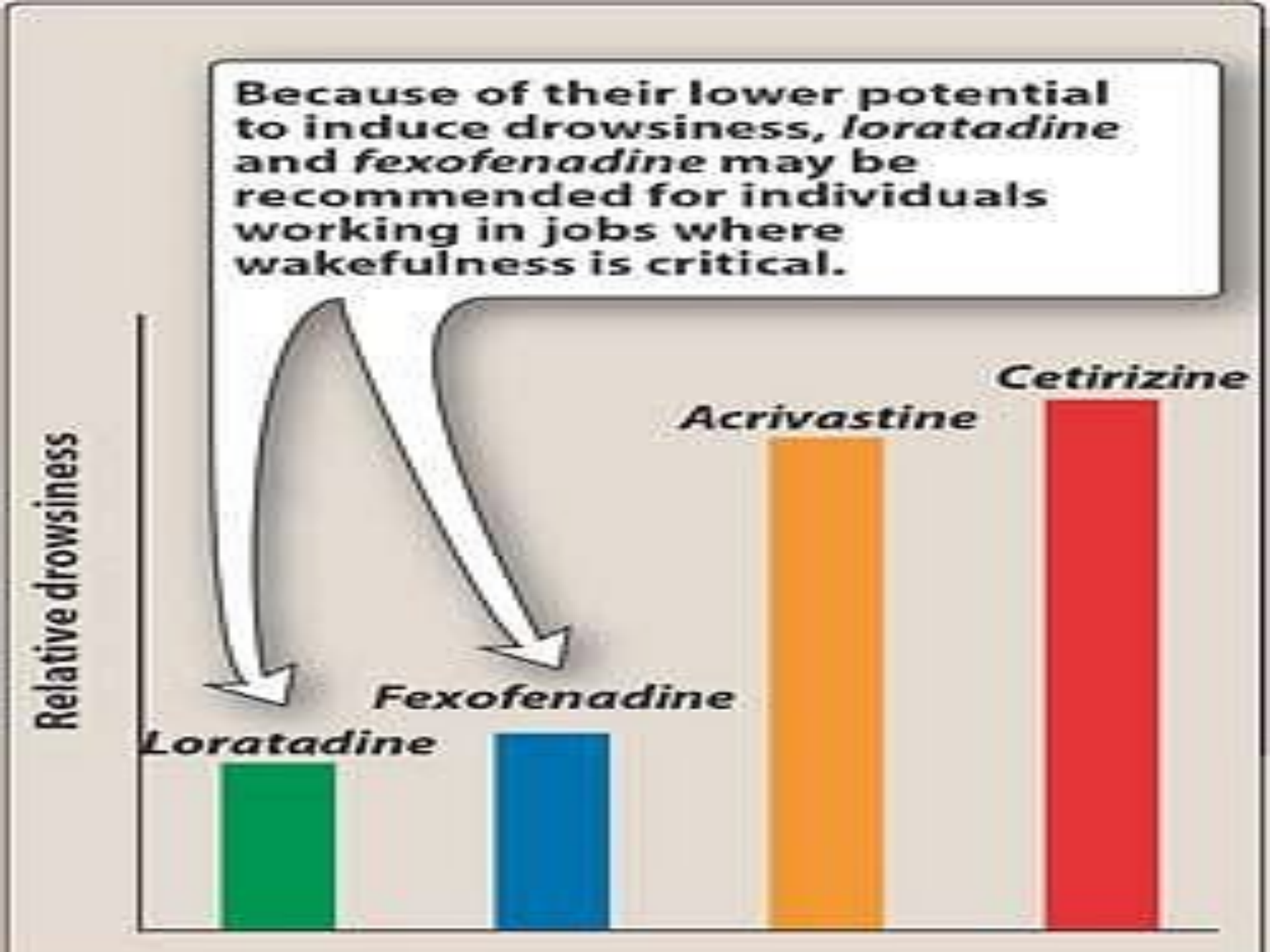
bs they act on **CTZ and vestibular** system(bs contain it histamine receptors). They are usually not effective if symptoms are already present and, thus, should be taken **prior** to expected travel.

Cinnirizine treat vertigo.

Meclizine is also useful for the treatment of vertigo associated with vestibular disorders

3- insomnia : bs of Somnifacients(sleep producing effect) although they are not the medication of choice, many first-generation antihistamines, such as diphenhydramine and

doxylamine have strong sedative properties and are used in the treatment of insomnia. They are contraindicated in the treatment of individuals **working in jobs** in which **wakefulness** is critical


Because of their lower potential to induce drowsiness, *loratadine* and *fexofenadine* may be recommended for individuals working in jobs where wakefulness is critical.
Relative drowsiness
Loratadine
Fexofenadine
Acrivastine
Cetirizine

The **second-generation** antihistamines have **no value** as **somnifacients**.

4- **Parkinsonism**: promethacine and diphenhydramine (Bs of anticholenergic activity by action of antihista. On other types of receptor bs of non specifity) (anticholenergic activity)

5- to **Increase appetite** **(also** bs of blocking of serotonin receptors) e.g cyproheptadine

Side effects:

1- sedation (bs it cross BBB)

2- dry mouth, blurred vision and retention of urine (bs anticholenergic effect bs they are non specific).

3- drug interaction like potentiation of the effects of other CNS depressants.

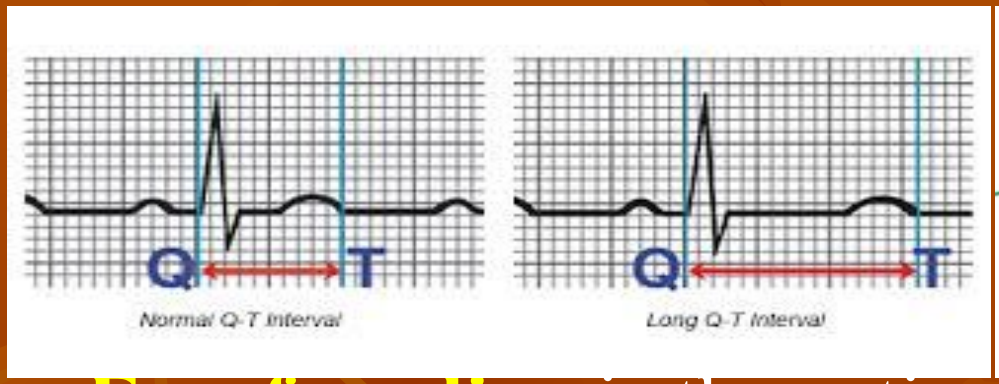
4- overdose : acute poisoning is relatively common in young children. **Dangerous effects** of acute poisoning are those on the **CNS**. If **untreated** the patient may experience a deepening coma and collapse of the cardiorespiratory system

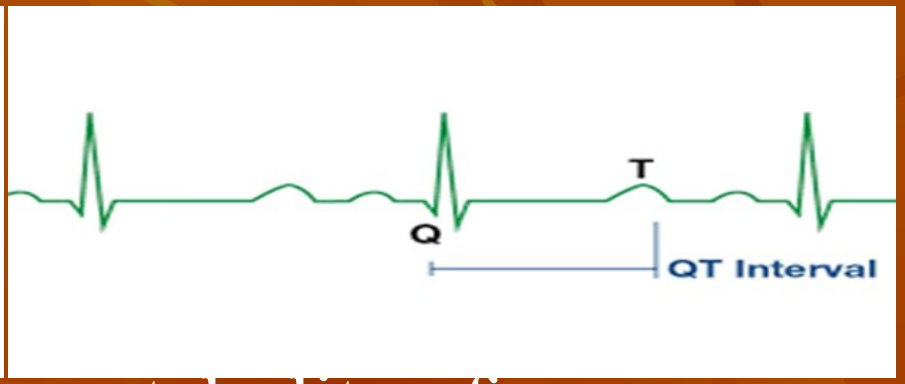
5- Topical **formulations** of diphenhydramine can cause local hypersensitivity reactions such as contact dermatitis.

6-**Terfenadine** can **prolong the QT interval**. This occurs when

A- The recommended dose is **exceeded**

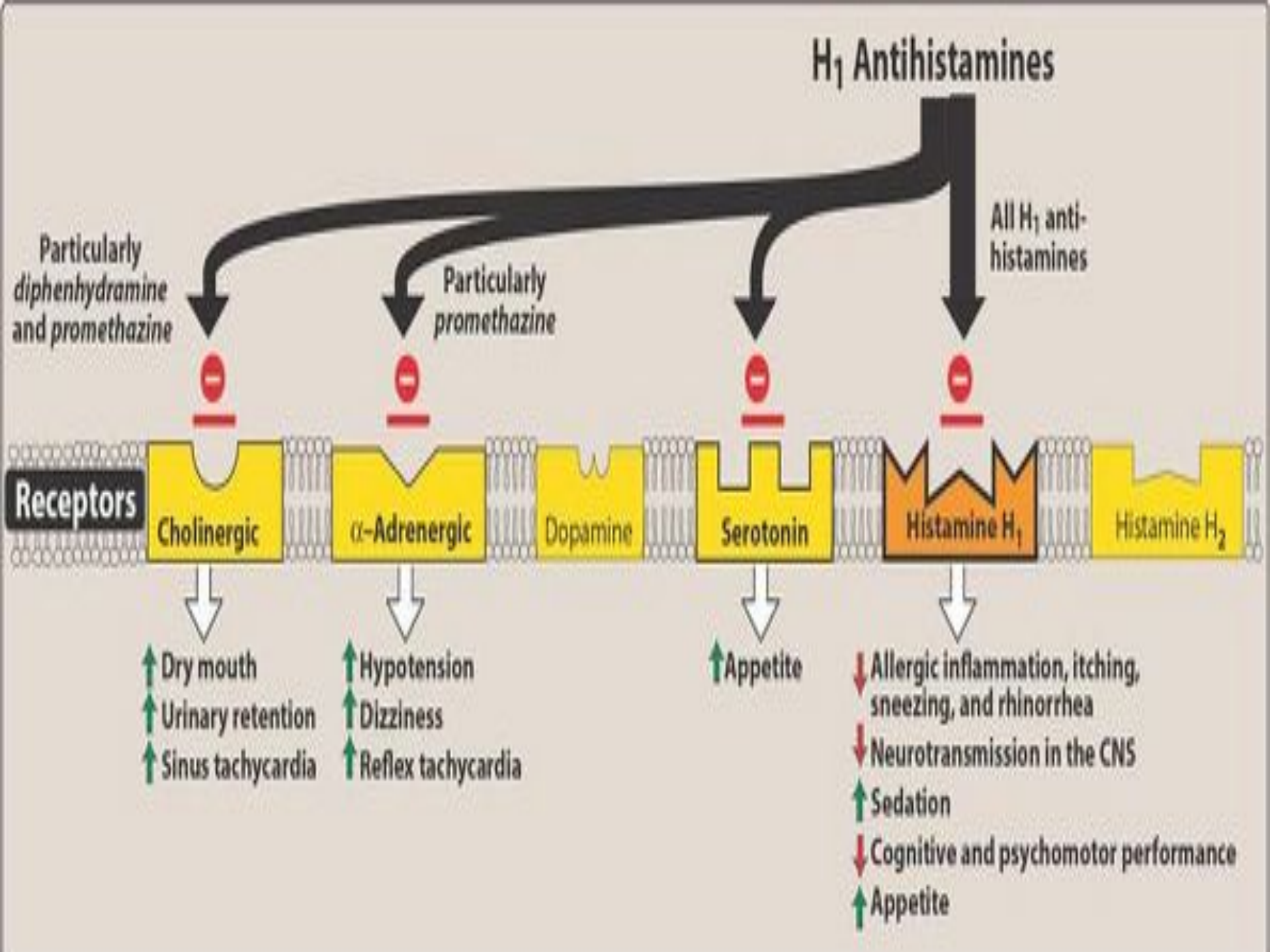
B- Drug is **administered with** substances that **block hepatic metabolism**(erythromycin and ketoconazole).





Fexofenadine is the active metabolite of terfenadine and appears safe in this respect

7- others are mentioned in following diagram:


H1 Antihistamines
Particularly diphenhydramine and promethazine
Particularly promethazine
All H1 anti-histamines
Receptors
Cholinergic
α-Adrenergic
Dopamine
Serotonin
Histamine H1
Histamine H2
Dry mouth
Urinary retention
Sinus tachycardia
Hypotension
Dizziness
Reflex tachycardia
Appetite
Allergic inflammation, itching, sneezing, and rhinorrhea
Neurotransmission in the CNS
Sedation
Cognitive and psychomotor performance
Appetite

Histamine H2 receptor blockers:

They block H2 receptors with no or little H1 receptors, thus it will inhibit gastric acid secretion.

Bs there are inhibitors of gastric acid secretion, so they used in treatment of peptic ulcers **e.g.**

cimetidine

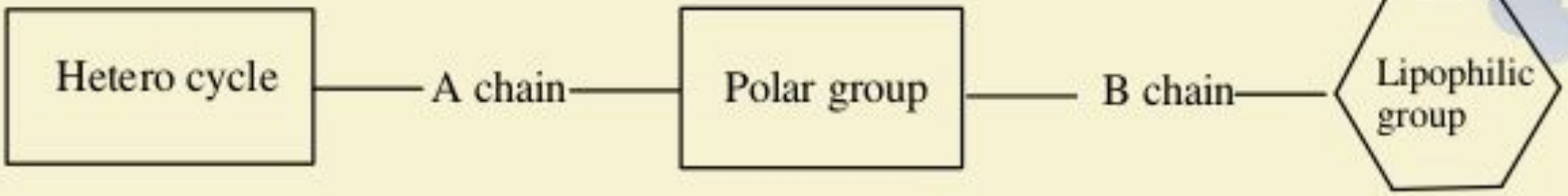
famotidine

nizatidine

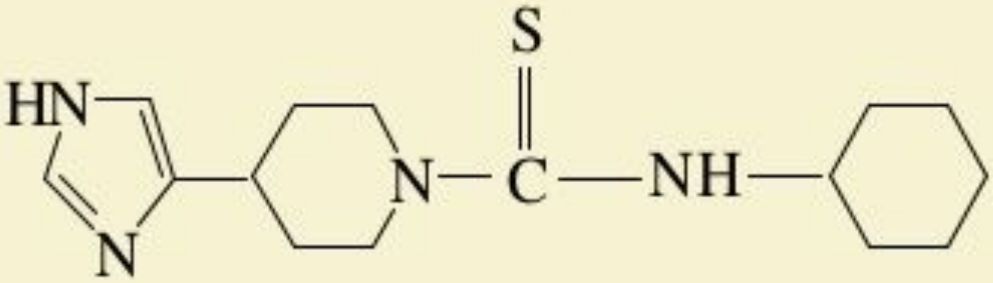
ranitidine.

H_3 ANTAGONISTS

General structure:



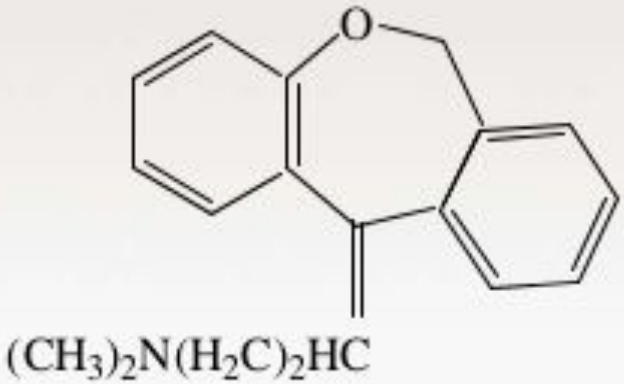
DRUGS:



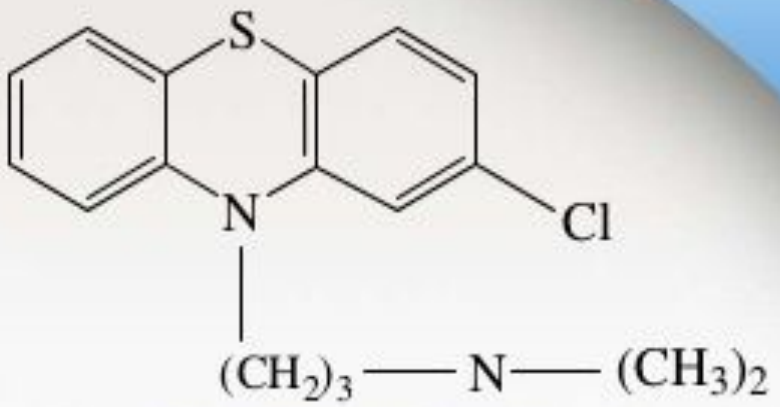
THIOPERAMIDE

- This THIOPERAMIDE was first potent H3 antagonist used to treat sleep disorders.

H_4 ANTAGONISTS



DOXEPINE



CHLORPROMAZINE

- This DOXEPINE, CHLORPROMAZINE are bind to the H4 receptor with high affinity.

Thank you

2022