Anti-histamines

Classify anti-histamines

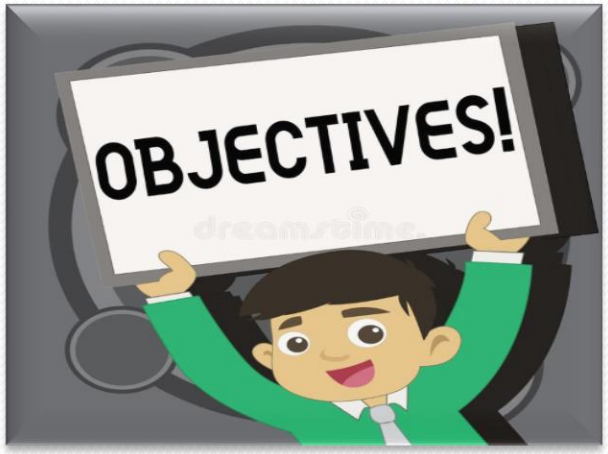
Differentiate between 1st & 2nd generation anti-histamines

Describe the pharmacologic effects of H_1 Receptor blockers

Describe the clinical uses of H_1blockers

Enlist the adverse effects of H_1blockers

Describe the drug interaction of H_1blockers



Histamine , serotonin and prostaglandins are called autacoids.

These heterogeneous substances have widely differing structures and pharmacologic activities.

They all have the common feature of being formed by the tissues on which they act; thus, they function as local hormones.

autos (self) and **akos (medicinal agent, or remedy)**

Histamine Cellular Responses

Allergic Reactions

Inflammatory Reactions

Gastric Acid Secretion

Neurotransmission

It itself has no therapeutic application but its antagonists have important clinical applications

Location of histamine

Practically present in all the tissues, but unevenly distributed.

Predominantly present in lungs , skin and GIT.

Found in the mast cell or basophills

Important component of venoms and insect sting secretions

- **mast cells, and basophils .**
- In mast cells, histamine is stored in granules as an inactive complex composed of histamine and the polysulfated heparin, along with an anionic protein.
- If histamine is not stored, it is rapidly inactivated by amine oxidase enzymes.

Release of histamine

- The release of histamine (in addition to the other mediators)may be the primary response to some stimuli.
- Stimuli causing the release of histamine from tissues include the
- **destruction of cells as a result of cold,**
- **bacterial toxins,**
- **bee sting venoms,**
- **trauma.**
- Allergies and anaphylaxis can also trigger release of histamine.

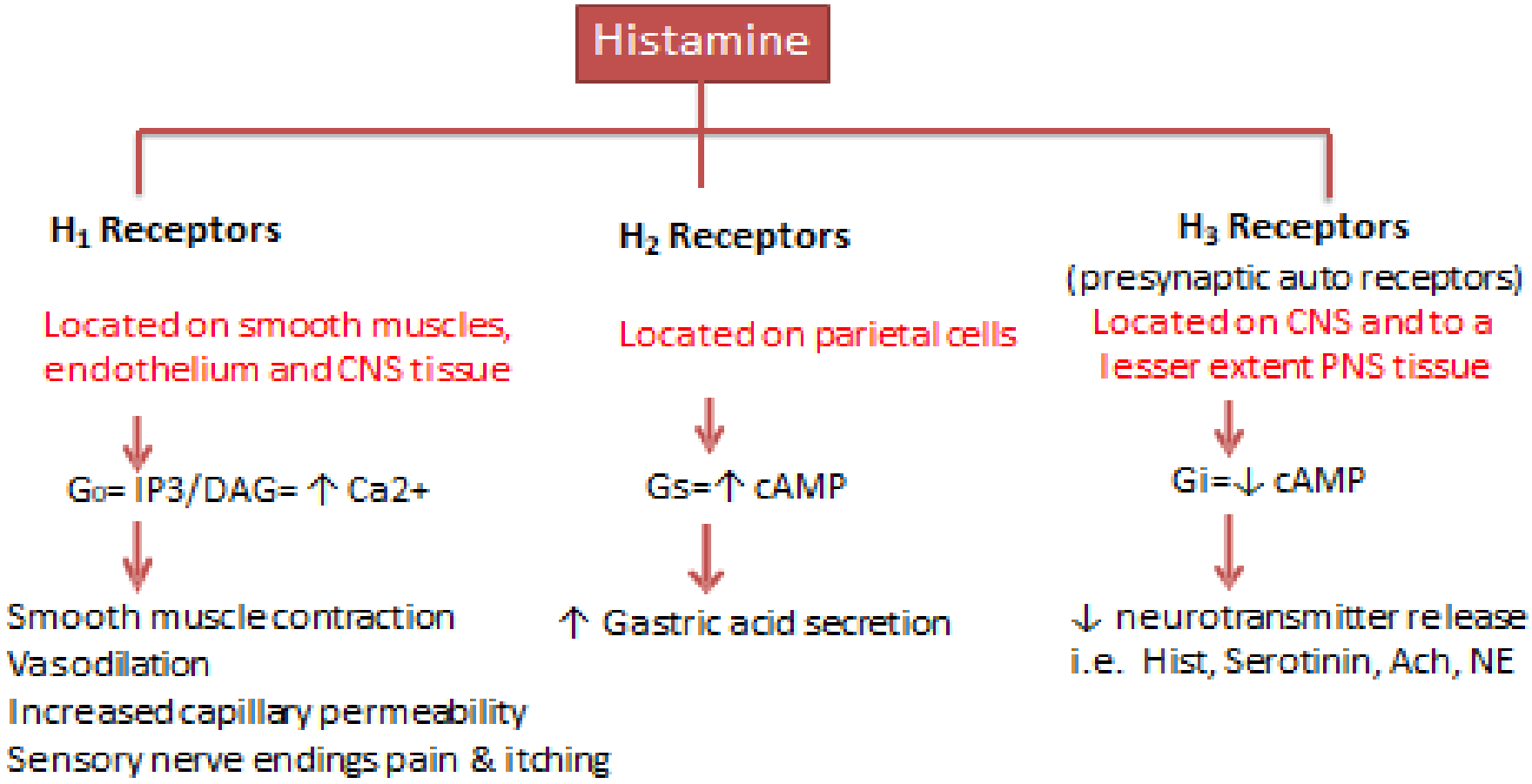
Histamine receptors

H_1 H_2 H_3 H_4

H1 , H2 are commonly found in different parts of the body and are targets of therapeutically important drugs

H3, H4 are located on few specific cell and their role as targets of different drugs is unclear

LOCATION OF HISTAMINE RECEPTORS AND MOA



Actions of Histamine (H_1receptors)

Exocrine excretion

Increases nasal secretions

Increases bronchial mucus. Therefore produces respiratory symptoms.

Bronchial smooth muscles:

Constriction of bronchial muscles----decreased lung capacity and symptoms of asthma

Intestinal smooth muscles:

Intestinal cramps and diarrhea

Sensory nerve endings

Causes itching and pain

CO

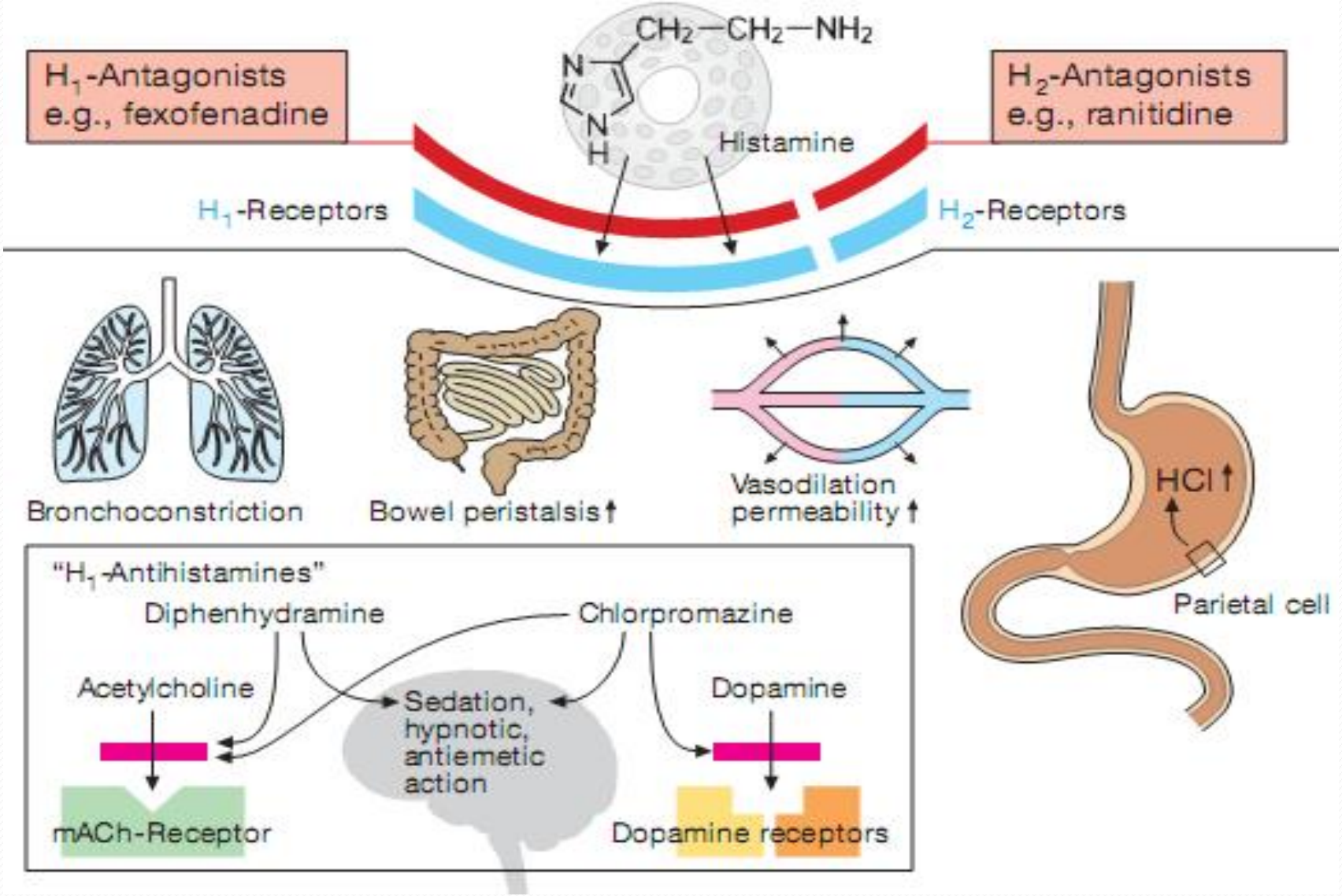
Action on CVS:
Vessels: decreases the resistance so lowers the blood pressure.(H1)
Heart : has positive chronotropic (H2) and positive ionotropic (H1, H2) effect.

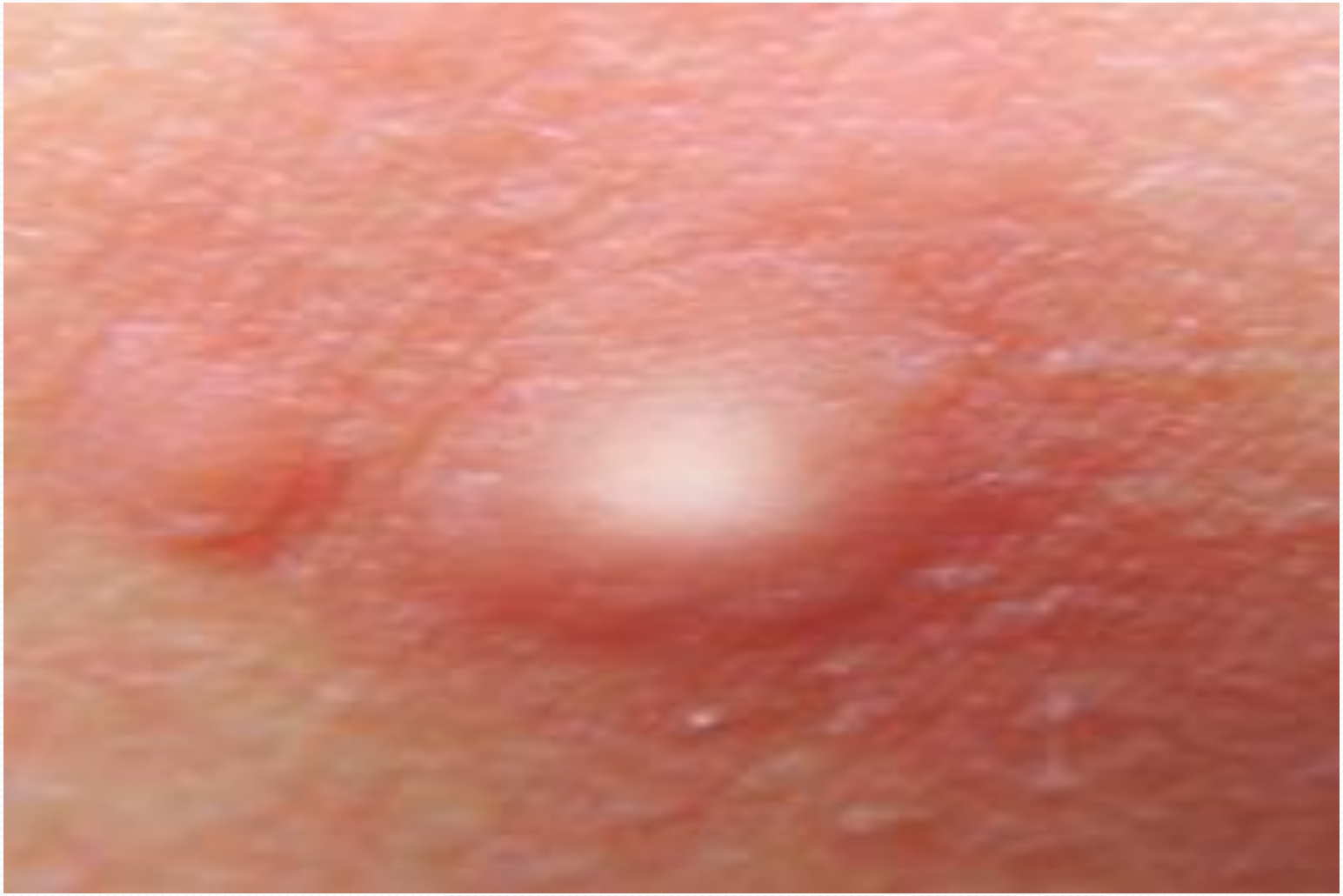
Action on skin
causes dilation and increased permeability of capillaries.
Increased leakage of fluid and proteins in the tissues

Classic triple response occurs
Wheal formation
Redness
Flare

Autonomic ganglia and Adrenal Medulla:
Adrenaline release = rise in BP

Action generated by H2 receptors -- increased gastric acid secretion


H1-Antagonists
e.g., fexofenadine
H2-Antagonists
e.g., ranitidine
CH2—CH2—NH2
N
N
H
Histamine
H1-Receptors
H2-Receptors
Bronchoconstriction
Bowel peristalsis ↑
Vasodilation
permeability ↑
HCl ↑
Parietal cell
"H1-Antihistamines"
Diphenhydramine
Chlorpromazine
Acetylcholine
Sedation,
hypnotic,
antiemetic
action
Dopamine
mACh-Receptor
Dopamine receptors



ROLE OF HISTAMINE IN ALLERGY AND ANAPHYLAXIS

- I/V injection of histamine produces symptoms similar to those associated with anaphylactic shock and allergic reaction .
- The symptoms produced are
- Contraction of air way smooth muscles
- Stimulation of secretions
- Dilatation of capillaries
- Increased permeability of vessels
- Sensitization of sensory nerve endings

Difference in response

- Symptoms of allergy & anaphylactic shock are due to release of mediators from their storage sites.
- Mediators released are histamine , serotonin, eosinophil chemotactic factor.
- Sometimes a local reaction is produced(skin reaction or respiratory reaction)
- Sometimes a full blown reaction anaphylactic reaction occurs.

- This difference in the intensity of reaction is due to

1. The site from where the mediators are released
2. The rate at which they are released.

For example if the rate of release is slow they will be readily degraded prior to entering the systemic circulation

But

If the rate of release is very rapid then they enter the systemic circulation in bioavailable form causing a full blown reaction

Classification Of Anti- Histamine

- **Physiological antagonist**

a. Epinephrine

- **Release inhibitors(mast cell stabilizers)**

a. Cromolyn
b. Nedocromil
c. Ketotifen
d. Olopatadine

- **Receptor blockers**

a. H_1 blockers
b. H_2blockers

Physiological antagonist

Histamine	**Bronchoconstriction & vasodilation (H_1)**
Epinephrine	**Bronchodilation β_2 Vasoconstriction α_1**

Release inhibitors

- Cromolyn
- Nedocromil
- Ketotifen
- Olopatadine
- These are mast cell stabilizers and inhibit the degranulation of mast cells.

Anti –Histamines
H_1-Receptor blockers

1st gen

- Ethanolamines → Diphenhydramine, Dimenhydrinate, Carbinoxamine, Doxylamine
- Ethylamine → Pyrilamine, Tripelannamine, Antazoline
- Alkylamine → chlorpheneramine, dexchlorpheneramine, Bronpheneramine
- Phenothiazine → Promethazine, Trimeprazine, Methdilazine
- Piperazine → Hydroxazine, Cyclizine, Meclizine
- Miscellaneous → Cyproheptadine, Phenindamine

2nd gen

Acrivistine, Citrizine, Loranitidine

3rd gen

Desloranitidine, Fexofenidine, Levocitrizine

H_2- receptor blockers

- Cimetidine
- Ranitidine
- Famotidine
- Nizatidine

2ND GENERATION IS BETTER THAN 1ST GENERATION?

First Generation

- Lipophilic, small size molecules, easily cross BBB
- Highly sedating agents
- Having anti-cholinergic, anti-alpha adrenergic and anti-serotinin effects
- Half-lives 4 –6 h

Second generation

- Less lipid soluble, large molecule size
- Less sedating
- No such effects
- Half lives of 12–24 h

Pharmacologic effects of H_1-Receptor blockers

Anti-allergic action

Anti-histamines suppress the manifestations of Type 1 hypersensitivity reactions by either inhibiting histamine release from granules or blocking histamine receptors

CNS depression

More with first generation as they crosses BBB

Sedation and drowsiness

Anti-muscarinic and alpha adrenergic blocking actions

Closely resemble muscarinic blockers and alpha blockers = blocks these autonomic receptors = Anti-muscarinic & anti-alpha adrenergic effects

More with first generation

Pharmacologic effects of H_1-Receptor blockers

Serotonin-Blocking Action

Block serotonin receptors of vomiting centre= treat emesis

More with first generation

Vestibular H-1 blocking action

Block H1 receptors of vestibule = treat vertigo

Sodium channel blocking action

Block Na channels in excitable membranes = Potent local anesthetics

Occasionally used in patients allergic to conventional local anesthetics

Therapeutic uses

- **Allergic and inflammatory conditions:** H_1receptor blockers in allergies act on IgE sensitized mast cells.
- They are the drug of choice allergic conditions in which the major mediator is histamine pruritis, urticaria, rhinitis, conjunctivitis and agioneurotic edema.
- They have not much role in allergic conditions where other mediators are predominating even if histamine is released abundantly like bronchoconstriction.
- **Common cold** : in this condition histamine is the major mediator so it is the drug of choice.
- **Pre-anesthetic medication**: ***promethazine*** is used for this purpose due to its antihistaminic and anti-cholinergic effects.
- **Motion sickness**: ***diphenhydramine , dimenhydrinate, meclizine , cyclizine , promethazine, hydroxazine***. They inhibit the nausea and vomiting responses from the CTZ, and vestibular pathway. This they do by blocking the H_1,M_1receptor in these regions

Therapeutic uses

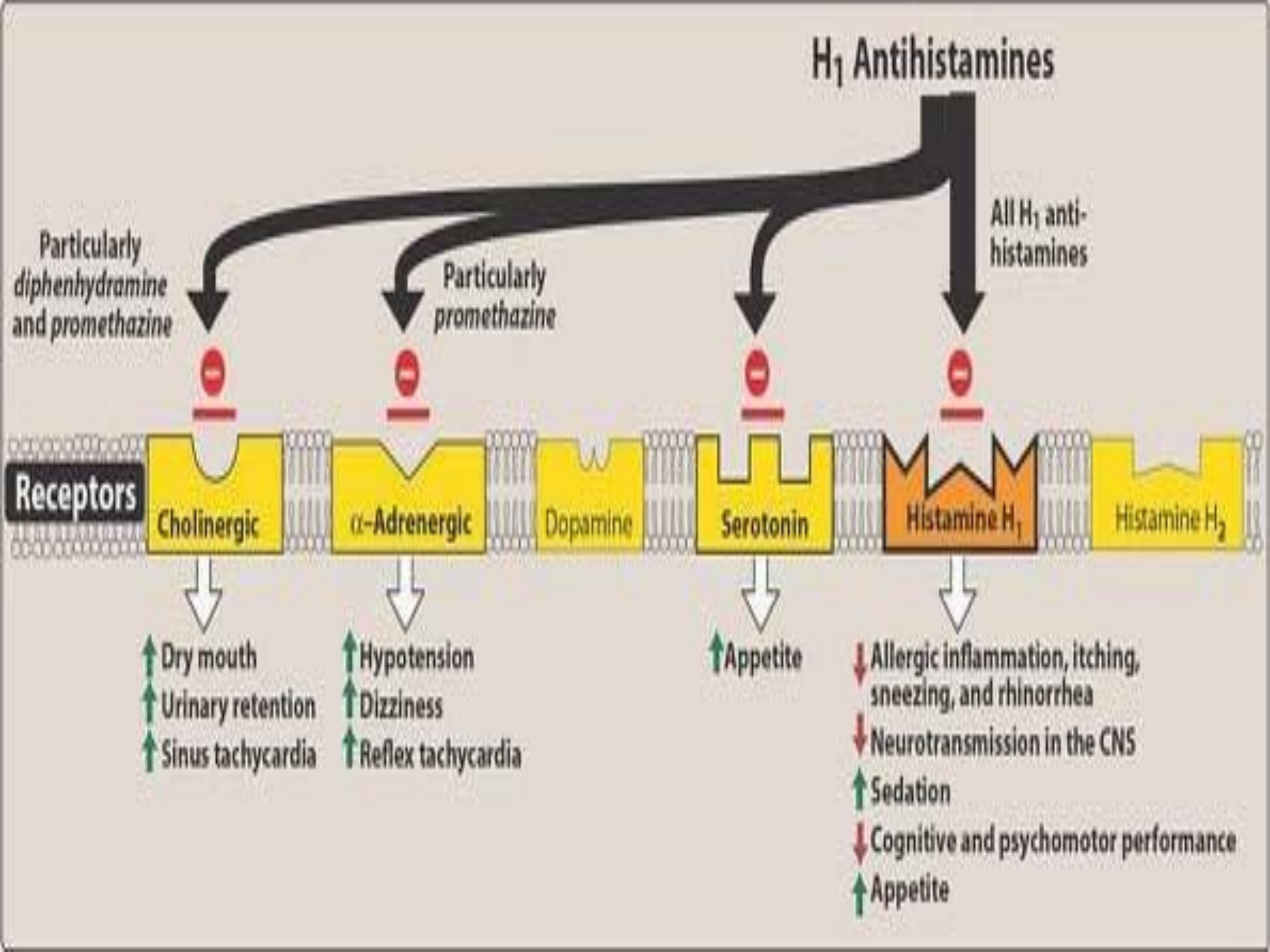
Parkinsonism: ***promethazine diphenhydramine or orphenadrine*** are used to control rigidity , tremors and sialorrhea of parkinsonism. This effect is produced due their anti-cholinergic and anti –histaminic properties.

Anti-histamines are used to **control blood transfusion reactions** as well as **saline infusion reactions** in adjunct with therapy for the control of anaphylaxis.

Vertigo: dimenhydrinate (gravinate)and meclizine are to control vertigo with menier's disease and other types of vertigo.

Anti-emetic in cancer chemotherapy and radiation induced vomiting. ***Promethazine*** is used for this kind of indication.

Sedative hypnotic: almost all the 1st generation drugs has this property of sedation. Chlorphenaramine (largectal) , promethazine (phenregun) and diphenhydramine (benedryl)are used to induce sleep especially in children for minor surgical procedures


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

Adverse effects

- 1st generation anti-histamines can cross the BBB and also has low specificity for the H_1 receptors ,they also act on adrenergic, cholinergic and serotonin receptors. Their interaction with other receptors is associated with side effects. Some of these effects may be unwanted and some may have therapeutic value. The intensity of adversities depends upon the extent interaction with other receptors, it also varies from individual to individual.

Adverse effects

1. **Sedation**: almost all the 1st gen drugs are associated with sedation . They bind to H_1receptors in the CNS and block the neurotransmitter effect of histamine there.
2. Other CNS effects include **tinnittus, dizziness, lassitude, uncoordination, blurred vision and tremors.** 2nd gen drugs are not associated with such effects.
3. **Anti-cholinergic effects**. Xerostomia, constipation, urinary retension, sinus tachycardia and blurring of vision.
4. **Teratogenic effects** : they have been observed to have Teratogenic effects in animals
5. **Adrenergic effects** : orthostatic hypotension, reflex tachycardia, dizziness.
6. **Anti-histaminic effects**: cognitive impairment
7. **Anti-serotonergic effect**: increased appetite.

DRUG INETRACTIONS

With CNS depressants = Potentiates depressant effects of 1st generation anti-histamines

With MAOIs= Potentiates anti-muscarinic effects of 1st generation anti-histamines

With Cholinesterase inhibitors = Cholinergic activity of these drugs may be decreased by anti-muscarinic effects of 1st generation anti-histamines

2nd generation anti-histamines

- They were developed in 1980.

1. Have no anti-cholinergic effects
2. Does not cross the BBB, hence minimal / or no drowsiness.
3. Does not impair psychomotor performance and also doesn't impair cognitive function
4. Are relatively expensive.

CETRIZINE **is** the most commonly used anti-histamine of this generation.

It not inhibits the binding of histamine to its respective receptor but also inhibits the release of histamine from storage sites.