Antihistamines poisoning

Histamine: a chemical messenger mostly generated in mast cells

- Mediates a wide range of cellular responses

  - Allergic and inflammatory reactions
  - Gastric acid secretion

  - Neurotransmission in parts of the brain.

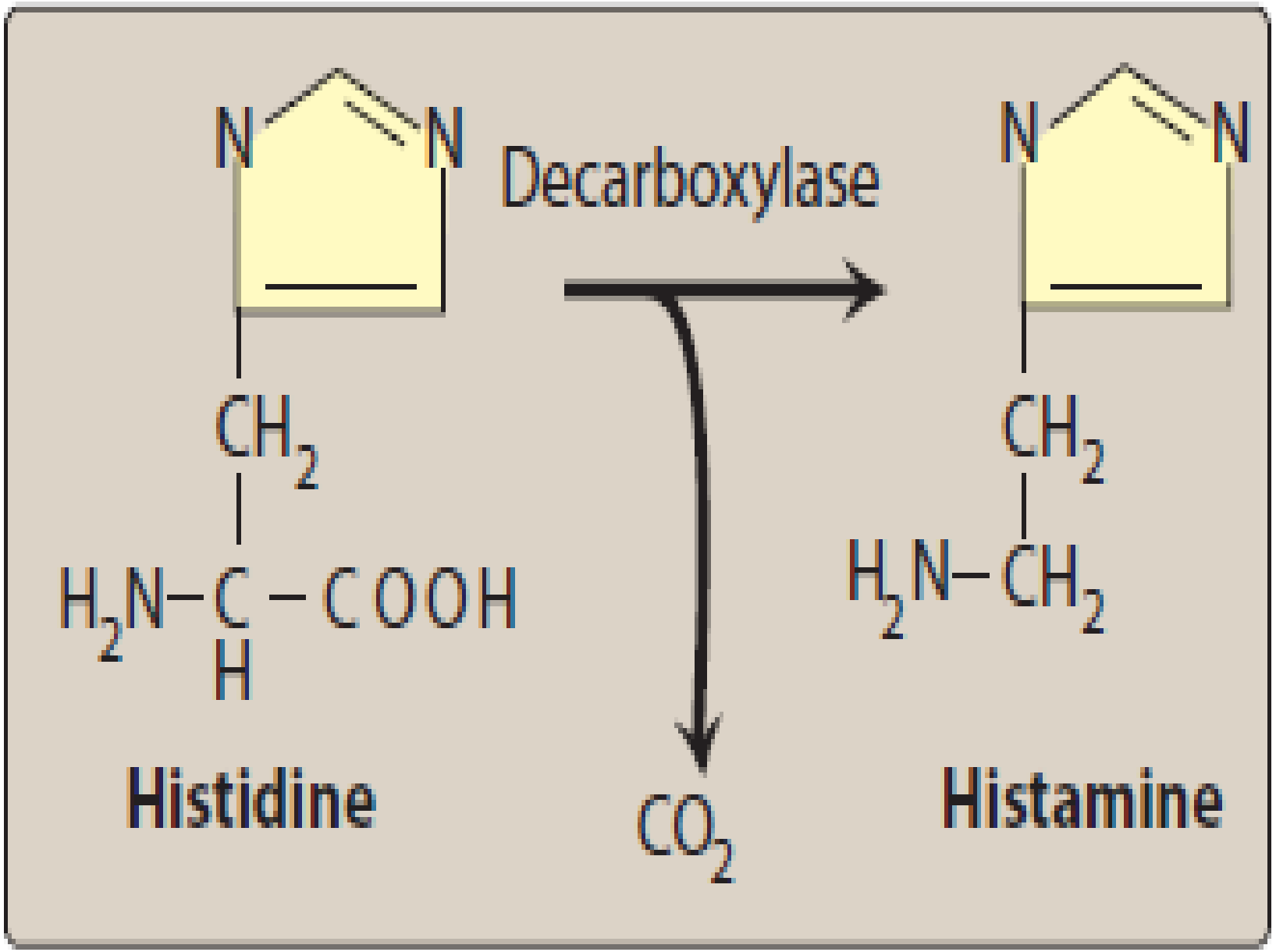
Histamine is present in practically all tissues, with significant amounts in the lungs, skin, blood vessels, and GI tract

- Found at high concentration in mast cells and basophils
- A neurotransmitter in the brain
- Also occurs as a component of venoms and in secretions from insect stings

Histamine is formed by the decarboxylation of histidine by histidine decarboxylase

- In mast cells, histamine is stored in granules

- If histamine is not stored, it is rapidly inactivated by the enzyme amine oxidase


N
N
Decarboxylase
CH2
H2N–C–COOH
H
Histidine
CO2
N
N
CH2
H2N–CH2
Histamine

Release of histamine

- Most often, histamine is just one of several chemical mediators released in response to stimuli

- The stimuli for release of histamine from tissues may include destruction of cells as a result of cold, toxins from organisms, venoms from insects and spiders, and trauma

- Allergies and anaphylaxis can also trigger significant release of histamine.

Azelastine
- Bepotastine
- Brompheniramine
- Cetirizine
- Chlorpheniramine
- Clemastine
- Cyclizine
- Cyproheptadine ?
- Desloratadine

- Diphenhydramine ?
- Dimenhydrinate
- Doxylamine
- Fexofenadine
- Hydroxyzine ?
- Ketotifen ?
- Levocetirizine
- Loratadine
- Meclizine
- Promethazine

Mechanism of action
Released in response to certain stimuli and binds to various types of histamine receptors (H1, H2, H3, and H4)

H1 and H2 receptors are widely expressed and are the targets of clinically useful drugs

H1 receptors are important in producing smooth muscle contraction and increasing capillary permeability

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

Can enhance secretion of proinflammatory cytokines in several cell types and in local tissues

H1 receptors mediate many pathological processes, including allergic rhinitis, atopic dermatitis, conjunctivitis, urticaria, bronchoconstriction, asthma, and anaphylaxis
Histamine stimulates the parietal cells in the stomach, causing an increase in acid secretion via the activation of H2 receptors.

The H1-receptor blockers can be divided into first- and second generation drugs.

- First generation drugs
  - Penetrate the CNS and cause sedation
  - Interact with other receptors, producing a variety of unwanted adverse effects

- Second-generation agents
  - Specific for peripheral H1 receptors
  - Do not penetrate the BBB causing less CNS depression than the first generation drugs
  - Desloratadine, fexofenadine and loratadine show the least sedation
  - Cetirizine and levocetirizine are partially sedating

- The action of all the H1-receptor blockers is qualitatively similar
- Block the receptor-mediated response of a target tissue
- Much more effective in preventing symptoms than reversing them

- Have additional effects due to binding to cholinergic, adrenergic, or serotonin receptors

- Cyproheptadine also acts as a serotonin antagonist on the appetite center, sometimes used off label as an appetite stimulant and in treating anorgasmy associated SSRIs

- Antihistamines such as azelastine and ketotifen also have mast cell-stabilizing effects

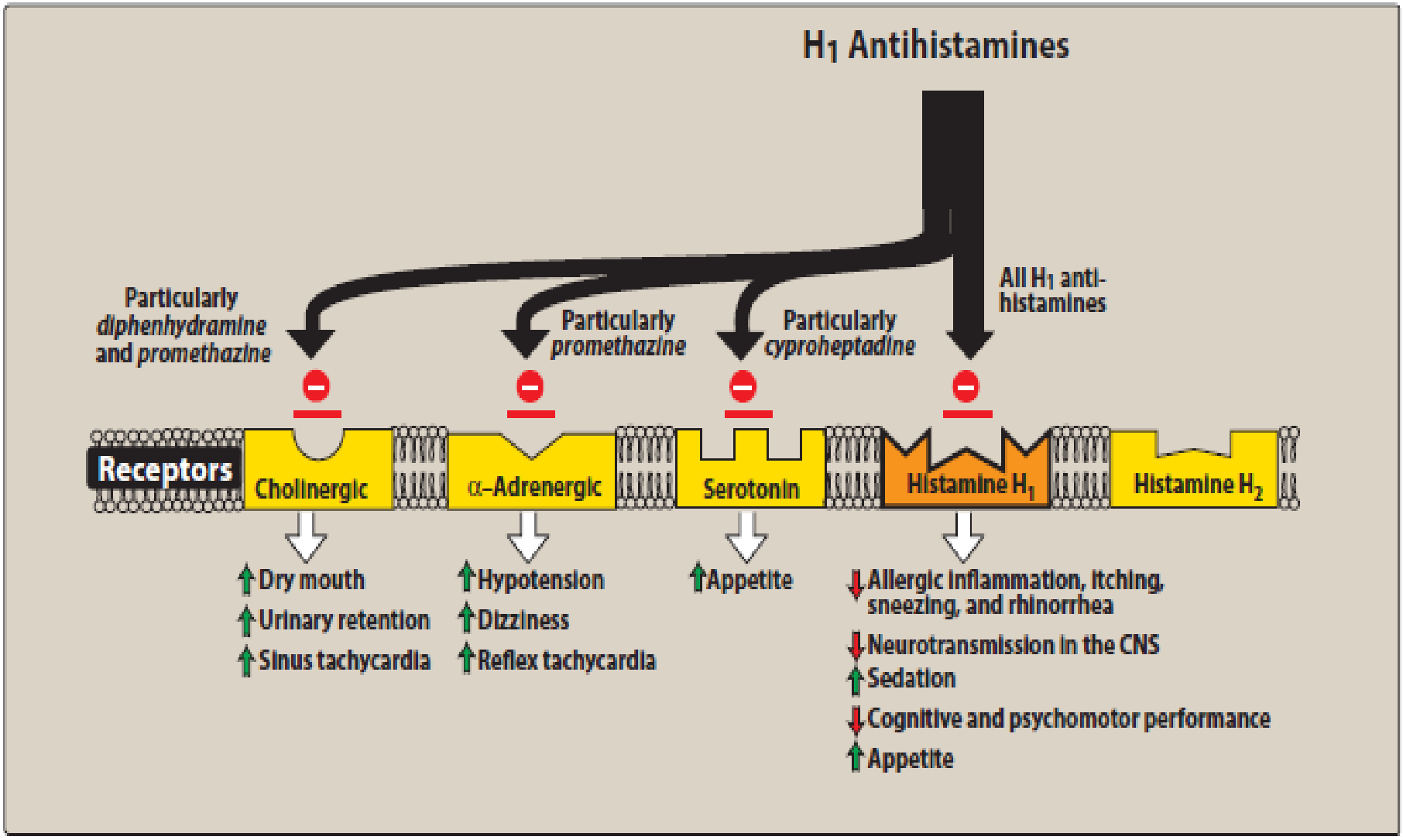


Figure 30.6

Effects of H_1 antihistamines at histamine, adrenergic, cholinergic, and serotonin-binding receptors. Many second-generation antihistamines do not enter the brain and, therefore, show minimal CNS effects.

Therapeutic uses

1. Allergic and inflammatory conditions

2. Motion sickness and nausea

3. Somnifacients

- First-generation H1-receptor blockers have a low specificity, interacting not only with histamine receptors but also with muscarinic cholinergic receptors, α-adrenergic receptors, and serotonin receptors

- The extent of interaction with these receptors and the nature of the side effects varies with the structure of the drug

- Some side effects may be undesirable, and others may be of therapeutic value
- Incidence and severity of adverse reactions for a given drug varies between individual subjects

- Sedation: (First-generation H1 antihistamines)
- Diphenhydramine may cause paradoxical hyperactivity in young children

- Fatigue, dizziness, lack of coordination, and tremors
- First-generation antihistamines exert anticholinergic effects, Dryness, blurred vision and retention of urine

- The most common adverse reaction associated with second-generation antihistamines is headache

- Topical diphenhydramine can cause hypersensitivity such as contact dermatitis when applied to the skin.

Drug interactions:

- Potentiation of effects of other CNS depressants, including alcohol
- Patients taking MAOIs should not take antihistamines
- 1st generation antihistamines with anticholinergic actions may decrease effectiveness of cholinesterase inhibitors

Overdoses:

- The margin of safety of H1-receptor blockers is relatively high, and chronic toxicity is rare
- Acute poisoning is relatively common, especially in young children
- The most common and dangerous effects of acute poisoning are those on the CNS, including hallucinations, excitement, ataxia, and convulsion
- If untreated, the patient may experience a deepening coma and collapse of the cardiorespiratory system

Toxicokinetics

Antihistamines are generally well-absorbed after ingestion.

Following oral administration, effects start within 15 to 30 minutes and are fully developed within one hour. Oral bioavailability is incomplete, ranging from 25 to 50%. Antihistamines are widely distributed throughout the body including the CNS, and are metabolised in the liver. Unchanged drug and metabolites are excreted in the urine.

Clinical (Toxic) Features

1. The toxicity of antihistamines is related to their anticholinergic (antimuscarinic) activity with the exception of toxic exposure to loratadine, terfenadine, and astemizole.

The action of acetylcholine at muscarinic receptors is blocked.

2. Most patients will present with CNS depression and anticholinergic manifestations (except those who have ingested cetirizine, loratidine, terfenadine, or astemizole).

Main symptoms include somnolence, lethargy, mydriasis, blurred vision, convulsions, hallucinations, extra-pyramidal movement disorders and psychosis.

3. Nystagmus and catatonic stupor have been described in relation to diphenhydramine overdose.

4. Other features include sinus tachycardia with hypo- or hypertension, dryness of skin and mucous membranes, cutaneous flushing, anhydrosis, hyperthermia, urinary retention, vomiting and diarrhoea/constipation.

5. Skin is usually flushed, warm and dry after overdose.
6. Hypertension is more commonly reported than hypotension. Tachycardia is also very common.

7. Rhabdomyolysis can occur. Acute renal failure has been reported in patients who developed rhabdomyolysis after overdose.

8. Terfenadine and astemizole are known to cause ventricular dysrhythmias and cardiac conduction defects. Several cases of prolonged QTc and QRS intervals and non-specific
ST and T-wave changes were reported following antihistamine overdoses.

9. Children are more likely to suffer from CNS stimulation, convulsions, and ARDS. Hallucinations, anxiety, restlessness, and agitation have been reported following overdoses of carbinoxamine, cetirizine, dexchlorpheniramine, diphenhydramine, doxylamine, pheniramine, and tripelennamine.

10. Cetirizine, loratidine, terfenadine, and astemizole cause much less CNS depression and anticholinergic effects.

Treatment:

If less than four times the maximum daily dose has been ingested by an asymptomic patient, he may be observed at home. If symptoms are present (other than mild somnolence), or if greater than four times the maximum daily dose has been ingested, the patient should be referred to a health care facility for evaluation:

1-Monitor vital signs, and watch for development of seizures, hyperthermia, and dysrhythmias.

2-Stomach wash, activated charcoal.

3-Whole bowel irrigation with polyethylene glycol electrolyte lavage solution should be considered in patients with extremely large ingestions and those involving sustained release preparations. However, cautions assessment of bowel motility is recommended prior to and during whole bowel irrigation.

Antihistamine overdose is frequently complicated by decreased bowel sounds, reduced gastrointestinal motility, or intestinal ileus.

4-Physostigmine for anticholinergic effects.

A-Dose:2mg (adult); 0.5mg (children), by slow IV push. It can be repeated at 5-10 minutes intervals if there is no significant improvement. Reversal within minutes of coma, arrhythmias, hallucinations, and other findings can be expected if the diagnosis is correct, and the patients has not suffered anoxia or other insult, or ingested a combination preparation.

B-Note: physostigmine should not be used in patients with suspected tricyclic antidepressant overdose, or an ECG suggestive of tricyclic antidepressant overdose (QRS widening, R wave in a VR). It can be precipitate seizures and intractable cardiac arrest.

5-Diazepam IV for agitation/psychosis, or convulsions. If seizures persist or recur administer phenobarbitone. Monitor for respiratory depression, hypotension, arrhythmias, and the need for endotracheal intubation.

6-Acute dystonic reactions to antihistamines may be treated with oral or intravenous diazepam.

7-Cooling measures for hyperthermia. Sponge patient with tepid water and use fans to maximize evaporative heat loss. Avoid phenothiazines.

8-Sinus tachyarrhythmias rarely require treatment. In agitated patients, sedation with benzodiazepines will generally control tachycardia. If severe tachycardia results in haemodynamic compromise or ischaemia, beta blocking agents may be used as a temporizing measure. A shortacting cardioselective agent such as esmolol is preferred. Use with caution in patients with asthma or COPD.

9-For mild/moderate asymptomic hypertension, pharmacologic intervention is generally not necessary. Sedative agents such as benzodiazepines may be helpful in treating hypertension and tachycardia in agitated patients, especially if a sympathomimetic agent is involved in the poisoning. For hypertensive emergencies (severe hypertension with evidence of end organ injury (CNS, cardiac, renal), or emergent need to lower mean arterial pressure 20 to 25% within one hour), nitroprusside is preffered. Nitroglycerine and phentolamine are possible alternatives.

10-Cardiotoxicity necessitates careful cardiac monitoring. Dysrhythmias can be corrected with IV magnesium sulfate (2 to 6gm in adults; 25to50mg/Kg in children), or lignocaine. Cardioversion can be tried.

Thank you