

Histamine & Drugs That Modify Its Effects

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Pharm 210, 2009

First topic for Exam 2

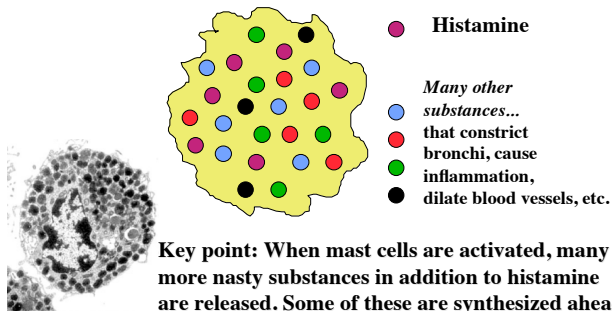
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Histamine

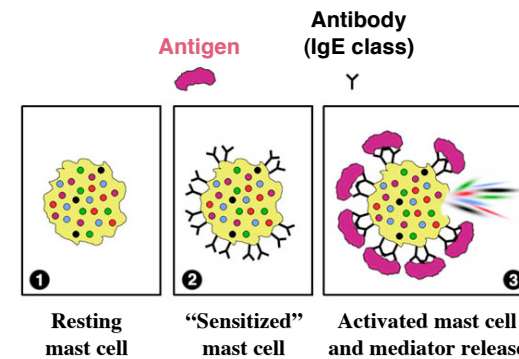
- An **autacoid**: a “local hormone”
- Main source **mast cells**
- Effects mediated by specific receptors
- Physiologic - pathophysiologic roles
 - Tissue repair, inflammation
 - Control of local blood flow
 - Contributor to allergic, anaphylactic reactions
 - Regulates gastric acid secretion
 - May be neurotransmitter in CNS

Mast Cells



Key point: When mast cells are activated, many more nasty substances in addition to histamine are released. Some of these are synthesized ahead of time, waiting for cell activation. Others are synthesized right at the time they get released. But antihistamines block *only* the effects of histamine.

Mediator Release From Immunologically-Sensitized Mast Cells (i.e., an “allergic reaction”)

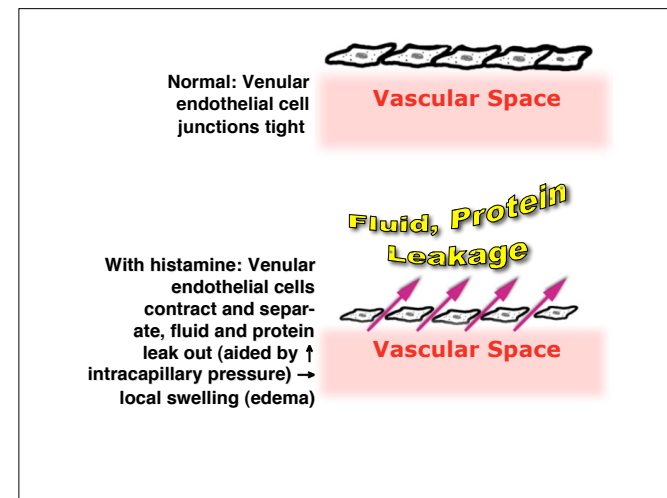
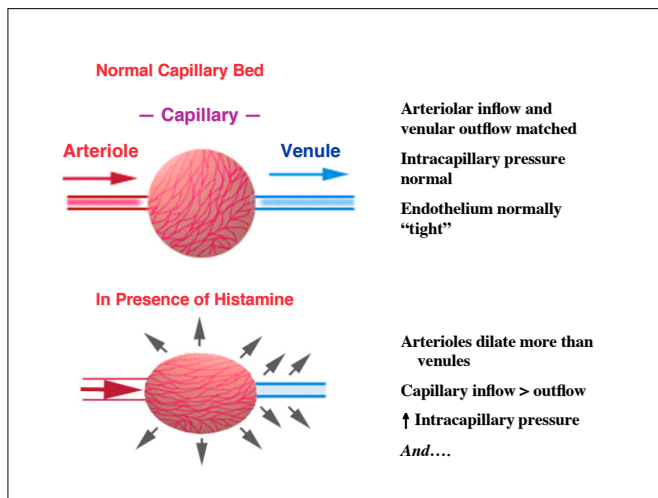


Other Mechanisms of Histamine Release

- **Physiologic:** Other mechanisms release histamine (only) from sites such as gastric acid-secreting cells, certain cells in brain
- **Drug-induced:** e.g., by tubocurarine, morphine, and a few others; by various plant toxins and animal venoms (e.g., snake, insect)
- **Other:** trauma, including burns

H Receptors and Some Responses They Control

- **H-1**
 - bronchoconstriction
 - vasodilation (involves H-2 receptors too and “increased capillary permeability”)
- **H-2**
 - ↑ gastric acid secretion
 - ↑ HR, contractility
 - vasodilation (involves H-1 receptors too)



The “Triple Response of Lewis” From Intradermal Histamine Injection*

- **Flush** (localized “capillary dilation”)
- **Flare** (more widespread arteriolar dilation, blood flows in to area; probably histamine-triggered neural reflex)
- **Wheal** (fluid, protein leakage from capillaries causes central blanched area)
- **Plus pain, itching, as sensory nerves are irritated**

*This is quite similar to happens with a mosquito bite, which causes localized histamine release from mast cells.

H-Receptor Antagonists (Blockers)... The “Antihistamines”

- **H-1 Blockers**

Overall Prototype
Diphenhydramine (BENADRYL)

- **H-2 Blockers**

Prototype: Cimetidine (TAGAMET)

All are *competitive antagonists* of the effects of histamine on its receptors.

The Two “Generations” of H-1 Blockers

- **“1st Generation”**
 - Older ones
 - Many drugs, many OTC, many found in multi-ingredient cough/flu/cold remedies
 - Many useful and some deleterious “other” properties
- **“2nd Generation”**
 - Newer, fewer
 - Narrower spectrum of activity, which is mostly advantageous

Diphenhydramine (1st Gen.) Actions

- **Blocks H-1 receptors (not H-2)**
- **Strong atropine-like actions (muscarinic blockade)**
 - Can be clinically useful or harmful
- **Sedating**
- **Good local anesthetic activity**

Diphenhydramine: Some Uses

- Relief of mild allergy S/Sx (urticaria, itching, etc.) — can be given orally or topically for allergic reactions involving the skin
- Sedative/hypnotic (sleep aid)
- Local anesthetic (topical or parenteral)
- Management of Parkinson's Disease

Histamine Blockers For...

- Anaphylaxis?
- Asthma?
- The common cold?

H1 Blockers (cont'd)

- SE: **same as atropine**, + sedation
- CI: "ditto"
- OD: "ditto" and...
 - adults: progressive CNS depression
→ coma, seizures
 - children: seizures come quickly
- TX of OD: same as atropine (!)

Topical Diphenhydramine- containing Lotions, Gels, Creams

Usually 1%-2% diphenhydramine

Not for blistered, raw, oozing skin

Limit use to 7 days

Other 1st Generation H-1 Blockers

- Several chemical classes, many drugs...
- Cause varying degrees of
 - sedation
 - atropine-like actions
 - other special/other effects that may be beneficial or deleterious...

Older H-1 Blocker Classes, Examples, and Key Properties -- I.

- **Ethanolamines:** diphenhydramine, doxylamine
 - Considerable sedative, anticholinergic activity
 - **Dimenhydrinate**, a diphenhydramine derivative, has good anti-motion sickness activity

*For info only; specific groups, properties not testable

Older H-1 Blocker Classes, Examples, and Key Properties -- II.

- **Ethylenediamines:** pyrilamine
 - Less sedating than ethanolamines, but still problematic
- **Piperazines:** cyclizine, meclizine, hydroxyzine
 - Moderate sedation, good antiemetic and anti-motion sickness
 - Teratogenic

*For info only; specific groups, properties not testable

Older H-1 Blocker Classes -- III.

- **Alkylamines:** brompheniramine, chlorpheniramine
 - Slight but definite sedation
 - Found in many OTCs
- **Phenothiazines:** promethazine
 - Significant sedative, antimuscarinic, antitussive, antiemetic, anti-motion sickness activity
 - Most phenothiazines are used as antipsychotic drugs

*For info only; specific groups, properties not testable

Some 2nd Generation H-1 Blockers

Fexofenadine (ALLEGRA)

Loratadine (CLARITIN)

Desloratadine (CLARINEX)

Cetirizine (ZYRTEC)

others

2nd Generation H-1 Blockers

- Block only H-1 receptors
- Basically *no* atropine-like SE/CI
- “Not sedating” ... at usual recommended doses
- Used for allergies, instead of an older H-1 antihistamine
- OK for asthma (no atropine-like problems) but aren’t cures or primary therapy
- OD -- little good info on what happens

H2 Blockers

Cimetidine (TAGAMET), Ranitidine (ZANTAC),

Nizatidine (AXID), Famotidine (PEPCID)

- None block H-1 (or ACh) receptors
- Uses, SEs, CIs are very different from those of any H1 blocker
- Main use: **suppression of gastric acid secretion in peptic ulcer disease, gastroesophageal reflux disease (GERD)**
- Cimetidine is most widely used example of a drug that causes drug-drug interactions (inhibits P450)... the other drugs listed above interact with very few other drugs

Mast Cell “Stabilizers”

Cromolyn (INTAL)

Nedocromil (TILADE)

- Block **release** of H, *other mediators*, from mast cells,
- Do not block histamine receptors
- Uses:
 - **prophylaxis** of asthma s/sx (orally inhaled)
 - prophylaxis of seasonal allergy (hay fever) S/Sx (nasal, ocular — nasal drops, eye drops)
- SE: **wheezing, coughing**
- Toxicity/OD: **Almost none**