**Injection of histamine** → replicate anaphylactic shock

- Decrease systolic & diastolic BP
  - Direct vasodilator action on arterioles & precapillary sphincters
- Increase in heart rate
  - Stimulatory actions of histamine on the heart & reflex tachycardia
- Flushing, warmth, headache
- Edema
- Mild wheezing to bronchoconstriction

**Central roles of histamine**

- Histaminergic neurons found in tuberomammilary body (hypothalamus)
  - Neuroendocrine control
  - Cardiovascular regulation
  - Thermal & body weight regulation
- Histamine also increases excitability of cortical neurons & contributes to arousal
  - Activity of histaminergic neurons decreases as sleep progresses

**Histamine mediated allergic response:** TYPE 1

- Large amount of histamines in mast cells
- Mast cells have IgE antibodies attached to their surface membranes → degranulate "explosively" when exposed to the appropriate antigen
- Histamine acts locally to inflame tissues & increase blood flow
- Sufficient release of histamine → anaphylactic shock symptoms

**(Other) peripheral actions of histamine**

- Gastric acid release: stimulated by release of histamine
  - Found in enterochromaffin-like cells and in neurons of enteric nervous system
- Inflammation: chemotactic attraction for inflammatory cells
  - Injury-related release of histamine causes local vasodilation, leakage of plasma containing mediators of acute inflammation, and antibody invasion
- Pain: stimulates sensory nerve endings mediating pain and itching

**Histamine receptors**

| | | |
|---|---|---|
| H1 | Bronchial smooth muscle | Bronchoconstriction |
| | GI smooth muscle | Contraction |
| | **Endothelium** | • **Vasodilation (release of NO)**<br>• **Separation of endothelial cells → plasma protein estravasation (urticaria or hives)** |
| | Brain | Arousal |
| | **Nerve endings** | **Pain, itch** |
| H2 | **Gastric mucosa** | **Stimulates parietal cells (H+)** |
| | Cardiac muscle | Increased contractility & pacemaker rate |
| | Vascular smooth muscle | Vasodilation |
| | Mast cells | Decreases histamine release |
| | Brain | Decreases histamine release |
| H3 | **Brain**, myenteric plexus, nerve endings | **Presynaptic: decreases neurotransmitter release** |
| H4 | Eosinophils, neutrophils, CD4 T cells | Chemotactic effects |
| | **Nerve endings** | **Pain, itch** |

**Histamine agonists**

**Inhaled:** diagnosis of bronchial hyperreactivity (asthma or cystic fibrosis)

- Pts may be 100 – 1000x more sensitive to histamine
- Risky to use this method of diagnosis

**Betahistine:** H1 agonist/H3 antagonist

- Increases cerebral blood flow (microcirculatory vasodilator)
- Anti-vertigo effect (dizziness), used in Maniere's disease

**H3 receptor agonists:** proposed to be potentially useful for allergic rhinitis (inhibition of vasoactive neuropeptide release) and for treatment of pain

**H1 receptor antagonists**

**First-generation**: diphenhydramine, chlorpheniramine, doxylamine

- Relatively strong sedative effects (penetrate CNS)
- Anticholinergic (antimuscuranic) effects

**Uses**

- Allergic reactions – urticaria
- Prevent motion sickness – antinausea
- Treatment of N & V – antiemetic
  - Doxylamine & diphenhydramine for pregnancy (morning sickness)
- Sedation – mild insomnia (temporary)
  - Tend to cause daytime drowsiness
  - Continuous use → tolerance
  - Children occasionally manifest excitation rather than sedation
- Local anesthesia – pts allergic to conventional LAs
  - Diphenhydramine more potent than some LAs (ex// procaine)

**Adverse effects**

- 50% get unwanted sedation
- Therapeutic efficacy varies → diminished efficacy with continued use (switch types)
- Urinary retention & blurred vision (anticholinergic)
- Orthostatic hypotension (α-adrenergic antagonist)

**Second-generation:** Loratadine, Cetirizine, fexofenadine

- Poor CNS penetration leads to little or no sedation

**Uses:** allergic conditions such as hay fever, allergic rhinitis, and chronic urticaria

**Adverse effects**

- 7% get unwanted sedation
- Therapeutic efficacy varies and diminished efficacy with continued use (switch types)

**Urticaria (hives):** localized vascular reaction (PRISH)

**Types**

- Hypersensitivity Type I = IgE
  - IgE immune complexes cross-link Fc receptors on mast cells & basophils
  - Causes degranulation with histamine release = Triple Response of Lewis
- Non-immune-mediated
  - Complement-mediated (viral/ bacterial)
  - Physical (pressure, cold)
  - Chronic (idiopathic)

**S/S**

- Transient appearance of smooth red flushed wheals
- Itchy
- Associated with increased mast cell numbers & tissue histamine levels (other mechanisms possible)
- Self-resolving within hrs – days (chronic = > 6 wks)
- Rare → anaphylaxis

**Treatment**

- Avoid known triggers & aspirin, alcohol, NSAIDs (makes worse)
- 1st line: H1 antagonists
  - 1st generation faster onset
  - 2nd generation preferred
- 2nd line: add H2 antagonist (?)
- Chronic: daily dosing of 2nd gen H1, can add H2 antagonist (and may also use oral corticosteroid)

**H2 receptor antagonists:** Ranitidine, Famotidine

**MOA**
- Competitive inhibition at parietal cell H2 receptors
- Reduced histamine released from ECL cells
- Block direct stimulation of parietal cell by histamine

**Uses**
- Peptic & duodenal ulcers (2nd line)
- Gastric-esophageal reflux disease
- Dyspepsia (indigestion)
- Stress-related ulcers

→ Suppress basal (90%) and meal-stimulated (60-90%) acid secretion in a linear, dose-dependent manner
→ Overall each dose will suppress acid release by 50% for 10h

**Adverse effects**
- 3% get diarrhea, headache, fatigue, myalgias or constipation
- Confusion, hallucinations, agitation may occur in ICU or elderly patients
- Bradycardia (result of blocking H2 receptors) can occur with rapid IV infusion
- Crosses placenta and accumulates in breast milk

**H3 antagonists:** enhance histamine release from histaminergic neurons → clinical trials
- Alzheimer's disease
- Obesity (weight loss)
- ADHD
- Parkinson's Disease
- Schizophrenia
- Narcolepsy
    - Pitolisant (inverse agonist): wake promotion; applied locally causes itch

**H4 antagonists:** developed but not yet in clinical use (proposed uses)
- Inflammatory bowel diseases (Crohn's, Ulcerative colitis): link b/w elevated histamine & IBD proposed
- Allergic asthmas (COPD): increased levels of histamine in asthmatic airways correlated with severity
    - H4 antagonists effective in animal models
    - H1 & H2 antagonists little or no effect in asthma
- Pruritus
    - Itch proposed to be transmitted from skin to spinal cord by C fibers (unmyelinated, < 2 m/s)
        - Histamine-dependent (acute) – mechanically insensitive C fibers (CMi)
            - H1 antagonists effective for acute itch but not chronic itch
            - H4 antagonists effective for pruritus
        - Histamine-independent (chronic) – polymodal C fibers