PULMONARY PHARMACOLOGY

ANATOMY & FUNCTION
Main players: alveoli, bronchioles, pulmonary artery/vein

RESPIRATORY DISORDERS

ASTHMA
- Smooth muscle of bronchioles constrict \(\rightarrow\) ↓volume \(\rightarrow\) ↓air flow into lungs
- Triggers: airborne irritants, allergens, emotional stress

COPD
- Chronic bronchitis
  - Irritant exposure (e.g. smoking) \(\rightarrow\) ↑mucus production \(\rightarrow\) clogged bronchioles \(\rightarrow\) ↑coughing
- Emphysema
  - Imbalance between \textit{neutrophil elastase} vs. α-1-\textit{anitrypsin}
  - Cigarette smoke \(\rightarrow\) ↑\textit{neutrophil elastase} \(\rightarrow\) destroys elastin in alveoli walls \(\rightarrow\) ↓wall elasticity \(\rightarrow\) exhalation>inhalation \(\rightarrow\) ↓volume of exchanged gas

Symptoms
- Bronchoconstriction, inflammation, mucus \(\leftrightarrow\) All of which are drug targets

DRUG THERAPY

BRONCHODILATORS
- MOA: relax smooth muscles \(\rightarrow\) dilate airways \(\rightarrow\) improve airflow
- β adrenergic agonists
  - Sympathetic agonists: \(\beta_2\) causes a lot of relaxation, \(\alpha_1\) causes a little contraction
  - SE: insomnia, anxiety, tremor, uterine muscle relaxation, insulin release, muscle/liver vasodilation
  - Formulation: inhalers (MDI or DPI)
  - Duration of action determined by \(\beta_2\) specificity
  - Short-acting
    - Albuterol, salbutamol
    - Available as racemic mixtures but only one enantiomer active (difficult to separate)
    - Acute relief of bronchospasm in both asthma and COPD
    - Dosage forms: MDI, nebulizer, oral, IV
    - SAR: aromatic (phenolic), hydroxylated, nitrogen functional group, levo- enantiomer
  - Long-acting
    - Formoterol, salmeterol, clenbuterol, bambuterol
  - Ultra long-acting
    - Indacaterol
  - Epinephrine/adrenaline
    - EpiPen: OTC auto-injector for acute allergic reactions
    - Non-selective agonist of all adrenergic receptors
    - Quick acting: t½ of 2 minutes
- Anticholinergics
  - Muscarinic antagonists: blocked M3 causes dilation
  - (−)M3 receptor \(\rightarrow\) ↓cGMP \(\rightarrow\) dilation of bronchoconstrictor muscles + ↓mucus \(\rightarrow\) bronchodilation
  - 4° amides: when inhaled, only topical and not systemic because not absorbed well so ↓SE
  - Non-selective antimuscarinics
  - Can be used in combination with fenoterol and albuterol
  - Long acting: tiotropium
  - Short acting: ipratropium
ANTI-INFLAMMATORY AGENTS

Inflammation is a long-term delayed response: airway inflammation, airflow obstruction, hyperresponsiveness

- **Corticosteroids** (glucocorticoids)
  - Are also leukotriene modifiers, but not only so
  - Delayed systemic action, no immediate or direct action on airway smooth muscles
  - Effects: ↓inflammation, ↓lung damage, ↓airway narrowing, ↓mucus, ↓cytokine expression, ↑β2 receptor expression
  - Synthesis: adrenal cortex
  - MOA: binds to & activates GC receptor → ↑expression of anti-inflammatory proteins in nucleus → ↓expression of pro-inflammatory proteins in cytosol
  - MOA: ↑Lipocortin-1 (annexin-1) → ↓phospholipase A₂ → (--)eicosanoid production → (--) leukocyte inflammatory events
    - (--) Inflammatory events: ↓prostaglandins, ↓leukotrienes, ↓COX expression
  - **Systemic**: hydrocortisone, prednisone, dexamethasone, prednisolone, methylprednisolone
  - **Inhaled**: beclomethasone, budesonide, flunisolide, fluticasone, triamcinolone

- **Leukotriene modifiers** (LRTA)
  - Montelukast, zafirlukast, zileuton
  - Montelukast & zafirlukast MOA: blocks leukotriene D4 from binding to receptor in lungs/bronchial tubes → ↓bronchoconstriction & ↓inflammation
  - Zileuton MOA: (--) 5-lipoxygenase → (--) leukotriene synthesis
  - Kid friendly: virtually no SE, oral administration
  - Theophylline
    - Hardly used anymore due to too many SE
    - Competitively & non-selectively blocks phosphodiesterase → (--)leukotriene synthesis

- **Mast cell stabilizers**
  - Blocks Ca²⁺ channels → ↓Ca²⁺ influx → stops vesicles from fusing to cell membranes → ↓mast cell degranulation → mast cell stabilization → prevent release of histamine & other inflammatory mediators
  - Treatment of asthma (COPD not an allergic response)

- **Human immunoglobulin antibody**
  - Omalizulab (Xolair)
  - Treatment of moderate to severe allergic asthma that can’t be controlled with even high dose steroids
  - Super expensive: $10,000 to $30,000/year
  - Not immediate relief
  - Subcutaneous injection every 2-4 weeks
  - Recombinant IgG1k monoclonal antibody that binds to IgE so that IgE can’t bind to allergens