Asthma and Drug Treatment

Learning Outcomes:

- Appreciate the different processes involved in airway obstruction.
- Explain the mechanism of action and adverse effects of the drugs used to treat asthma.
- Explain the rationale for drug combinations in asthma.

Understanding Asthma:

- Asthma is a heterogeneous syndrome with overlapping phenotypes based on allergic or non-allergic responses.
- It is classified based on a person's response to medication, with some types not responding well to steroids.

Factors That Influence Asthma Development

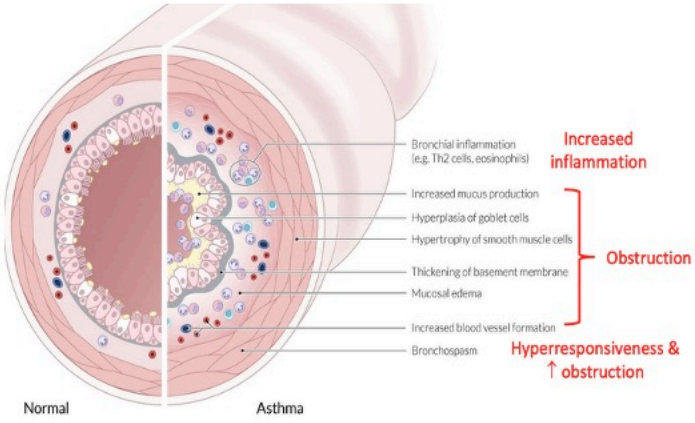
- Host factors
    - Genetic: atopy, airway hyperresponsiveness
    - Gender: males are more likely at younger age (<14), females more likely after
    - Obesity
- Environmental factors
    - Indoor/outdoor allergens
    - Chemical irritants
    - Tobacco smoke
    - Air pollution
    - Respiratory infections

Predominant characteristics of allergic (TH2-type) asthma:

- Asthma involves airway obstruction, airway hyperresponsiveness, and chronic eosinophilic airway inflammation
- Allergens trigger an immune response involving APCs, naive T lymphocytes, Th2 cells, cytokines IL-4 and 13, and IgE production from B lymphocytes that bind to mast cells
- IL-5 is also released which recruits eosinophils, leading to bronchoconstriction, mucus secretion, and edema in the airways.

Structural Changes in Asthma:

- Increased inflammation, angiogenesis, fibrosis, hypertrophy of airway smooth muscles, hyperplasia of goblet cells.
- This results in a narrowed airway lumen, increased mucus secretion, and airway hyperresponsiveness.



Diagnosis and Monitoring:

- Spirometry measures lung function, showing a decline in forced expiratory volume (FEV) with bronchoconstrictor mediators like histamine and methacholine.
- Airways in asthma contract more easily and at lower concentrations of bronchoconstrictors, leading to exaggerated responses.

Drug Treatment for Asthma:

- Prevent development of allergy: no drugs yet
- Prevent or reverse the airway obstruction: target smooth muscle contraction (relievers and preventers) or target airway inflammation (preventers)
    - Targeting airway inflammation: chronic inflammation and structural changes sensitive to glucocorticoids (corticosteroids)
- Combinations of drugs are often necessary due to the dual aspects of airway constriction and inflammation in asthma.
- Adverse effects of drugs are related to their mechanisms of action and should be understood in context.

Drug Delivery

- Either inhaled or swallowed
- Benefits: direct, quick, less dose (less absorption/distribution), minimise systemic absorption and side effects

Beta-2 Adrenoceptor Agonists

- B2-agonist or circulating adrenaline -> GPCR -> AC -> cAMP -> PKA -> decreased cytoplasmic Ca2+ -> relaxation of ASM
    - Counteract increased Ca2+ from bronchoconstrictors (functional antagonism)
- Further inhibits (dephosphorylates) myosin light chain kinase (MLCK) = no contraction

Short-Acting Beta2 Adrenoceptor Agonists (SABA; Reliever)

- Acute symptom relief or exercise-induced bronchoconstriction
- Must be used with an inhaled corticosteroid (maintain beta-2-adrenoceptor level)
- Frequent use associated with poor outcomes
    - beta2 -adrenoceptor downregulation, ↓ bronchodilator response
- Rapid (2-5 min) onset of action
- Duration of 2-4 h (diffusion, not metabolism)
- Examples: Salbutamol, terbutaline

Long-Acting Beta2 Adrenoceptor Agonists (LABA; preventer)

- Prophylaxis (prevent bronchoconstriction)
- Maintain ASM tone in relaxed state = chronic bronchodilation
- Always combined with ICS (glucocorticoid) in single actuator
- Examples:
    - Salmeterol (slow onset, 12 h duration), formoterol (rapid onset, 12 h duration)

Adverse Effects and Precautions

- Common side effects of beta agonists include tremors, palpitations, headache, tachycardia, and non-selective effects (e.g. B1 activation in heart)
- Precautions needed for patients with hypertension, heart failure, diabetes, or use sympathomimetic amines

Inhaled Corticosteroids

- Mimic action of cortisol
- Glucocorticoid receptors dimerise upon activation and translocate to nucleus
    - Glucocorticoid has to be lipid soluble
- Increased anti-inflammatory gene expression and decreased inflammatory gene expression
    - Anti-inflammatory genes: annexin-1 and beta2-adrenoceptors
    - Inflammatory genes: inflammatory enzymes (COX-2, PLA2), cytokines (TNFa), and adhesions molecules (ICAM-1)
- Main preventative (prophylactic) treatment – regular daily treatment
- Slow onset of action (gene transcription), used for long-term management of asthma.
- Can be inhaled corticosteroids (ICS) or systemic corticosteroids (oral, tablet, liquid); systemic usually for severe asthma or acute flare-up
    - Inhaled: well tolerated
        - Can cause hoarseness, weakness of voice (dysphonia = atrophy of vocal cords), and oral thrush (immunosuppression)
            - Mouthwash reduces local absorption
    - Oral: systemic effects; involved in the hypothalamic-pituitary-adrenal axis (stress)