Pharmacology of the Respiratory Tract: Asthma and Beta-agonists

Dr. Tillie-Louise Hackett
Department of Anesthesiology, Pharmacology and Therapeutics
University of British Columbia

Associate Head, Centre of Heart Lung Innovation, St Paul’s Hospital
Tillie.hackett@hli.ubc.ca
Aims of Lecture

Define Lung Structure
Define Asthma
  - epidemiology
  - alterations in lung function
Cellular mechanisms of disease
Action of short acting β-agonists (Salbuterol)
Action of muscarinic receptor blockers (Ipratropium)
The Respiratory System

70m² surface area for adequate gas exchange

AIRWAY STRUCTURE

Epithelium

Mesenchymal cells

Vasculature

Weibel, 2009, Swiss Med Wkly
The Respiratory System

GAS EXCHANGE STRUCTURE

~ 300 alveoli units in a human lung

Weibel, 2009, Swiss Med Wkly
Lung Structure

Weibel, 2009, Swiss Med Wkly
Lung morphometry

Weibel, 2009, Swiss Med Wkly
The prevalence of chronic Inflammatory Lung Diseases

COPD

Make up 90% of Health Care Costs
Asthma

- A chronic inflammatory disease of the airways characterized by reversible bronchospasm.
- Common symptoms include; wheezing, coughing, shortness of breath.
- Affects 300 million people worldwide
- 180,000 deaths annually
- 40% of Health Care costs
- 15–30% prevalence in children from developed countries
Etiology of Asthma:

- **Allergy: Hygiene Hypothesis**
  - 40% of the western world have some form of allergy
  - Changes in living conditions have contributed to allergen exposure
    - Clean houses, soft furnishings, central heating, pets (saliva, sweat, urine and dander)

- **Allergen proteases**
  - House dust mite: Live in bedding, carpets and feed off shed human skin. Fecal pellets (10-50 mm) contain large amounts of digestive enzymes
    - *Der P1* (*Dermatophagoides pteronyssinus*) is a cysteine protease which has been shown to penetrate the airway epithelial barrier and promote inflammation
  - Fel d 3 – Cat dander
  - PrtT – Aspergillus Fumigatus (mold)

- **Pollution** – High levels of PM10 are associated with asthma exacerbation
- **Genetics** - A child with one affected parent has ~25% risk of developing asthma, the risk increases to ~50% if both parents are asthmatic.
Bronchospasm

Before

10 minutes after allergen challenge
Bronchospasm

- Hyperreactivity of airways is an intrinsic part of the disease process and relates to disease severity
- Involves both large (>2 mm) and small (<2 mm) airways
- Extrinsic or allergic asthma
  - Dust mite, Pollens, Dander
- Intrinsic
  - Exercise, Cold air, Smoke
- Increased reactivity occurs following exposure to viruses and pollution
Clinical diagnosis of airway hyperreactivity

Methacholine Concentration (mg/ml)

FEV₁ (% change)

Asthmatic (moderate – severe)

Mild asthmatic

Normal

Normal = PC20 of > 16 mg/mL

Crosslinking of IgE leads to mast cell activation of Phospholipase C
- Inositol triphosphate
- Calcium signaling

Mast cells degranulate releasing a variety of mediators
Mast cell mediators
Mediator Effects in Asthma

### Preformed Mediators
- **Histamine**
- Chemotactic factors
- **Tryptase**
- **Prostaglandin D₂**
- **Prostaglandin E₂**
- **Thromboxane**
- **Bradykinin**
- **Platelet activating factor**

### Newly Formed Mediators
- **Superoxide**
- **Leukotrienes C₄, D₄, E₄**

### Cytokines
- Granulocyte–monocyte colony-stimulating factor
- **Interleukin-3**
- **Interleukin-5**

### Site of action

#### < 30 seconds after allergen exposure
- H₁ receptors on bronchial smooth muscle
- H₂ receptors on mucous cells
- Recruitment and priming of eosinophils
- Disrupt epithelial barrier, and possibly alter neuronal reflexes, enhancing bronchospasm

#### < 1 hour after allergen exposure
- Synthesis of arachidonic acid derivatives
  - Via lipoxygenase pathway LTC₄, D₄ and E₄ bind CysLT₁ receptor causing SM contraction
  - Via COX pathway PGD₂, PGE₂ bind D protanoid receptors on inflammatory cells

#### > 1 hour transcription of cytokines
- IL-4 also stimulates B cell secretion of IgE so amplifies the response

<table>
<thead>
<tr>
<th>Preformed Mediators</th>
<th>Newly Formed Mediators</th>
<th>Cytokines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histamine</td>
<td>Superoxide</td>
<td>Granulocyte–monocyte colony-stimulating factor</td>
</tr>
<tr>
<td>Chemotactic factors</td>
<td>Leukotrienes C₄, D₄, E₄</td>
<td><strong>Interleukin-3</strong></td>
</tr>
<tr>
<td>Tryptase</td>
<td></td>
<td><strong>Interleukin-5</strong></td>
</tr>
<tr>
<td>Prostaglandin D₂</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostaglandin E₂</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thromboxane</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bradykinin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet activating factor</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Effect</th>
<th>Site of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Airway smooth muscle contraction, mucus secretion</td>
<td>&lt; 30 seconds after allergen exposure</td>
</tr>
<tr>
<td>Chemotaxis of eosinophils and neutrophils</td>
<td>H₁ receptors on bronchial smooth muscle</td>
</tr>
<tr>
<td>Generation of bradykinin; degradation of vasoactive intestinal peptide</td>
<td>H₂ receptors on mucous cells</td>
</tr>
<tr>
<td>Cytotoxicity</td>
<td>Recruitment and priming of eosinophils</td>
</tr>
<tr>
<td>Airway smooth muscle contraction, mucosal edema, and mucus secretion</td>
<td>Disrupt epithelial barrier, and possibly alter neuronal reflexes, enhancing bronchospasm</td>
</tr>
<tr>
<td>Airway smooth muscle contraction</td>
<td>&lt; 1 hour after allergen exposure</td>
</tr>
<tr>
<td>Mucosal edema</td>
<td>Synthesis of arachidonic acid derivatives</td>
</tr>
<tr>
<td>Airway smooth muscle contraction</td>
<td>Via lipoxygenase pathway LTC₄, D₄ and E₄ bind CysLT₁ receptor causing SM contraction</td>
</tr>
<tr>
<td>Mucosal edema, airway smooth muscle contraction</td>
<td>Via COX pathway PGD₂, PGE₂ bind D protanoid receptors on inflammatory cells</td>
</tr>
<tr>
<td>Bronchoconstriction (?)</td>
<td>&gt; 1 hour transcription of cytokines</td>
</tr>
<tr>
<td>Stimulation, maturation, and priming of eosinophils</td>
<td>IL-4 also stimulates B cell secretion of IgE so amplifies the response</td>
</tr>
</tbody>
</table>
Asthma: Mucosal Oedema (1-2 hours)

- Recruited eosinophils enhance airway inflammation, mucus production, leading to cough and sputum production.
# Eosinophil mediators

<table>
<thead>
<tr>
<th>Mediator</th>
<th>Effects in Airway</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preformed Mediators</strong></td>
<td></td>
</tr>
<tr>
<td>Major basic protein</td>
<td>Cytotoxicity, epithelial cell damage</td>
</tr>
<tr>
<td>Eosinophil cationic protein</td>
<td>Cytotoxicity, neurotoxicity</td>
</tr>
<tr>
<td>Eosinophil-derived neurotoxin</td>
<td>Unknown</td>
</tr>
<tr>
<td>Eosinophil peroxidase</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Newly Formed Mediators</strong></td>
<td></td>
</tr>
<tr>
<td>Platelet activating factor</td>
<td>Bronchoconstriction (?)</td>
</tr>
<tr>
<td>Leukotriene B4</td>
<td>Mucosal inflammation, chemotaxis</td>
</tr>
<tr>
<td>Leukotriene C4</td>
<td>Airway smooth muscle contraction, edema, mucus secretion</td>
</tr>
<tr>
<td>15-hydroxyeicosatetraenoic acid</td>
<td>Activation of mast cells</td>
</tr>
</tbody>
</table>
But why is there persistent airflow limitation?

Melbourne asthma study

Airway Remodeling in Asthma

Normal Male 11Y

Asthmatic Male 11Y
Airway remodeling: Effects on lung function

Hyperplasia and hypertrophy of smooth muscle

- Thickening of airway wall even when relaxed
- Airway narrowing is exacerbated as small degree of muscle shortening causes a greater reduction in airway lumen

Goblet cell metaplasia

- Thickening of submucosal and increased mucus secretion into the airway lumen, reduced airway lumen

Fibrosis

- Extra cellular Matrix accumulation reduces airway size and elasticity
Asthma Treatment

Acute Inflammation

- Bronchoconstriction
- Oedema
- Secretions
- Cough

Chronic Inflammation

- Cell recruitment
- Epithelial damage
- Early structural changes

Airway Remodelling

- Cellular proliferation
- Extra-cellular matrix increase
Asthma Acute Therapies

- **Reliever Medications:**
  - Short-acting inhaled β2-adrenergic receptor agonists - (Salbuterol)

1) Binds β2-adrenergic G-protein coupled receptor

2) α-subunit of activated G-protein stimulates adenylyl cyclase to produce cAMP

3) In the muscle cAMP causes
   - decreased intracellular Ca2+
   - Activates protein kinase A

4) Results in smooth muscle relaxation
β2-adrenergic receptor agonists -

- The tertiary butyl group in salbutamol makes it more selective for β₂-receptors.
- The drug is sold as a racemic mixture the compound contains a chiral carbon which forms two stereoisomers that are mirror images of each other.

(S)-enantiomer (potential side effects) (bottom)
(R)-enantiomer shows activity (top).
Asthma Acute Therapies

- Ipratropium blocks muscarinic receptors, without specificity
- 4:1 ratio of muscarinic M₂ and M₃ receptors,
- G₉α coupled muscarinic M₃ receptor is responsible for airway smooth

1) Acetylcholine released from nerves binds m3Rs
2) Activated α subunit of Gq activates phospholipase C (PLC), which hydrolizes phosphoinositol 4,5- bis-phosphate (PIP₂) into 1,2- diacylglycerol (DAG), & inositol 1,4,5- trisphosphate (IP₃).
3) IP₃ promotes flux of Ca²⁺ channels.
4) Myosin light chain kinase activates cross-bridge cycling & muscle contraction.
Asthma therapies:
Controller Medications:

- **Inhaled glucocorticoids**
  - Bind to glucocorticoid receptors on cells recruiting fast array of transcription factors that act as feedback mechanism to regulate inflammation

- **Long-acting inhaled β2-agonists**
  - Used morning and night to provide 12 hour relief of symptoms. However due to sensitization of B2 receptor can lead to worsening of conditions and even death. FDA 2008 withdrew approval for use in children.

- **Anti-IgE antibodies (Omalizumab)**
  - Blocks allergens interacting with IgE preventing release of allergic mediators such as Histamine, leukotrienes and cytokines etc.

Slows Hydroxylation