Respiratory Pharmacology PCTH 400
Asthma and β-agonists

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Aims of Lecture

Distinguish between conducting and respiratory airways within the lung

Understand how aerosol particle size affects drug delivery to the lung

Describe the pathological mechanisms of bronchospasm in Asthma

Mechanism of action of β-agonists
The Respiratory System

70m² surface area

~ 300 million alveoli units in a human lung
Airway Structure

CONDUCTING AIRWAY STRUCTURE

Epithelium

Airflow

Mesenchyme

<table>
<thead>
<tr>
<th>Conducting airways</th>
<th>Acinar airways</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trachea</td>
<td>16 1</td>
</tr>
<tr>
<td>Bronchi</td>
<td>17 2</td>
</tr>
<tr>
<td>Bronchioles</td>
<td>18 3</td>
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<tr>
<td>Transitional bronchioles</td>
<td>19 4</td>
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<tr>
<td>Terminal bronchioles</td>
<td>20 5</td>
</tr>
<tr>
<td>Acinar airways</td>
<td>21 6</td>
</tr>
<tr>
<td>Respiratory bronchioles</td>
<td>22 7</td>
</tr>
<tr>
<td>Alveolar ducts</td>
<td>23 8</td>
</tr>
<tr>
<td>Alveolar sacs</td>
<td>24 9</td>
</tr>
</tbody>
</table>
Lung Parenchyma Structure

Weibel, 2009, Swiss Med Wkly
Blood - Gas Barrier structure

- Alveoli
- Alveolar Duct
Blood-Gas Barrier structure

Alveoli
## Advantages of pulmonary drug delivery

<table>
<thead>
<tr>
<th>Treatment of Respiratory Diseases</th>
<th>Treatment of systemic diseases</th>
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</table>
| Fraction of the systemic dose is required  
Oral salbutamol 2-4mg versus  
100-200µg with inhaler | Enormous absorptive surface area and  
highly permeable membrane  
“noninvasive needle free delivery” |
| Minimize risk of systemic side effects | Suitable for delivery of small molecules  
to very large proteins  
“slow mucociliary clearance” |
| Rapid clinical response | Low enzymatic environment |
| Bypass barriers to therapeutic efficacy;  
i.e. poor GI absorption and  
first-pass metabolism in the liver | Reproducible absorption kinetics  
Independent of interpatient variability of  
dietary complications, extracellular  
enzymes, GI absorption differences |
Particle size is an important variable for determining where the particle is deposited into the lung.
Most therapeutic aerosols are heterodisperse.
Lung Function Tests: Spirometry

- **FVC** - Forced Vital Capacity
  - the total volume of air that the patient can forcibly exhale in one breath.

- **FEV1** – Forced Expiratory Volume in One Second
  - the volume of air that the patient is able to exhale in the first second of forced expiration.

- **FEV1/FVC** – the ratio of FEV1 to FVC expressed as a fraction
Effect of drug aerosol's particle size on therapeutic efficacy

Percent improvement in FEV1

Cumulative dose of salbutamol (mg)

3.3 µm
7.7 µm
Asthma

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

Asthma Attacks

Allergic asthma
- Pollen
- Dust mite proteins

Non-allergic asthma
- Cold air
- Exercise
- Viral infection

- Hygiene Hypothesis - Changes in living conditions, exposure to allergens (proteases)
  - House dust mite Fecal pellets - *Der P1*
  - Cat dander - *Fel d 3*
  - Aspergillus Fumigatus (mold) – *PrtT*

- Type I hypersensitivity reaction
  
  [Diagram showing primary exposure to allergen, adaptive immune response, and generation of IgE]
Bronchospasm

Before

10 minutes after allergen challenge
Bronchospasm

- Hyperreactivity of airways relates directly to disease severity.

- Increased reactivity occurs following exposure to viruses, pollution and genetic background.
Clinical diagnosis of airway hyperreactivity

Methacholine Concentration (mg/ml)

FEV₁ (% change)

Asthmatic (moderate – severe)

Mild asthmatic

Normal = PC20 of > 16 mg/mL

Cellular mechanisms of bronchospasm

Crosslinking of IgE leads to mast cell activation

Mast cells degranulate releasing a variety of mediators
Early Phase: Mast cell mediators

Histamine
(Pre-formed mediator)

Cysteinyl Leukotrienes
( Newly formed mediator)

Bronchoconstriction

H1 receptor
Gq
Intracellular Ca2+
Smooth muscle cell
Contraction

Vasodilatation of arterioles
Type 1 activated endothelial cells recruit inflammatory cells
Late Phase: Mast Cell Mediators

- **TNFα** (Synthesized mediator)
- Type II activated endothelial cells recruit inflammatory cells
- Terminal arteriole
- Capillaries
- Post capillary venule

**Eosinophil**

- Recruitment & Activation
- IL-5
- GM-CSF (Granulocyte-macrophage colony stimulating factor)

**Cytotoxic Molecules**

- Major Basic Protein
- Eosinophil cationic Protein

**Damage of Airway Mucosa**

+ Bronchoconstriction (release of CySTLTs)
Airway closure in an asthma attack

- Bronchial tube
- Muscles – The bronchial tubes are wrapped with muscles
- Bronchiole – Smaller branches of the bronchial tubes
- Mucus lines the bronchial tubes
- Tight muscle
- Alveoli with trapped air
- Extra mucus

Airway Inflammation
Treatment for Asthma

Mild Asthma  - Intermittent attacks
              - Mild and not life threatening

Prescribe   - $\beta_2$ agonists to open airways and relieve symptoms
              - Salbutamol + Terbutaline
              - Active 1 – 4 hours

Severe Asthma - Persistent attacks
                 - Dangerous and life threatening

Prescribe   - Long acting $\beta_2$ agonists (LABAs)
              - Prophylactic treatment
              - Salmeterol + Formeterol
              - Active 12 hours
β₂ agonists to treat Allergic Asthma

Smooth Muscle Relaxation

B₂ Agonist

B₂ Adrenergic Receptor

GDP--

αₛ β γ

Heterodynamic G protein coupled receptor

GTP--

Off State

Active State

B₂ Adrenergic Receptors are primarily expressed in;

Vessels
Uterus
Airways
β₂ agonists to treat Allergic Asthma

Smooth Muscle Relaxation

1) Ca²⁺ efflux
2) Ca²⁺ influx
3) Decrease contractile proteins via Protein Kinase A

Adenylyl Cyclase

GTP -- αₛ

Catalyses cAMP production

Adenine + Pyrophosphate (PPI) → Cyclic Adenosine monophosphate (cAMP)
β₂ agonists to treat Allergic Asthma

Inflammation of the airway mucosa

Express B₂ Adrenergic Receptors

Stops production of pro-inflammatory mediators
  Histamines
  Leukotrienes
  TNFα
**β₂ agonists structure function**

**Epinephrine** – Binds β₁ and β₂ adrenergic receptors

**Albuterol** – Modifications to epinephrine Structure allows selectivity for β₂ effects

**Salmeterol** – Modifications inhibit degradation. Long lipophilic side chains attach to plasma membrane increasing duration of binding.
Common side effects of $\beta_2$ agonists

- Headache and dizziness
- Nausea, vomiting and diarrhea
- Anxiety, restlessness
- Nervousness or tremor (such as unsteady, shaky hands)
- Receptor desensitization with use of LABAs
- Side effects of $\beta_2$-agonists are more likely to occur when using the pill, liquid, or injectable forms than when using the inhaled form.