BACKGROUND ISSUES IN PULMONARY DRUG DELIVERY

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DRUGS ADMINISTERED BY INHALATION (1)
- Maintenance treatment of asthma and COPD
- Inhaled bronchodilators
  - Minimize symptoms
  - Reverse bronchoconstriction
- Inhaled anti-inflammatories
  - Corticosteroids
  - Cromolyn sodium
  - Control airway inflammation
  - Prevent asthma attacks
- Combination products
  - Bronchodilator + corticosteroid
  - e.g. Advair® Diskus®, GSK

Image courtesy of GlaxoSmithKline

DRUGS ADMINISTERED BY INHALATION (2)
- Other drugs for local action
  - e.g. Antibiotics, antiviral agents, mucoactive agents
  - Histamine, methacholine in bronchial challenge tests
- Systemic drug delivery
  - Using lung as a portal of entry to the body
  - Peptides, proteins
  - Analgesics and other drugs required to act rapidly

Image courtesy of www.inhalatorium.com

PULMONARY DRUG DELIVERY THROUGH HISTORY
- Accounts of pulmonary drug delivery in records of many ancient civilizations
  - Probably originated in traditional Ayurvedic medicine in India, about 2000 BC
  - Inhaling smoke from burning herbal preparations
  - Ebers papyrus, Egypt, 1500 BC
  - Galen (Rome): steam inhalations
  - Hippocrates (Greece): simple vapor inhaler
- 17th and 18th century Europe: Plague Doctor
  - Mask impregnated with spices or sulfur

Image courtesy of www.inhalatorium.com

EVOLUTION OF DRUGS AND INHALERS (1)
- First “inhaler” – John Mudge, 1778
  - Ceramic or metal construction
- British Pharmacopoeia, 1867
  - Inhaled hydrocyanic acid, creosote, chloroform, and iodine for asthma
- First atomizers in mid 19th century
  - Inhalation of atomized waters at European spas
  - Atomizers evolved into hand-held squeeze-bulb nebulizers

Images courtesy of www.inhalatorium.com

Image courtesy of Richard Dalby and Nicholas Miller
EVOLUTION OF DRUGS AND INHALERS (2)

- Asthma cigarettes, early 20th century
- Local and systemically acting drugs
  - Inhaled epinephrine (adrenaline) for asthma, 1910
  - Inhaled insulin first given 1925
  - Inhaled antibiotics, 1940s
  - Aerohalor® dry powder inhaler (Abbott)
- Lack of success owing to poor understanding of technical issues?

THE UPPER Airways


THE RESPIRATORY TRACT

WEIBEL MODEL OF LUNG (1)

- Bronchial tree – system of branching airways
- Weibel model (1963) - simple but very useful
  - 24 airway generations
  - Each airway branches into 2 airways in next generation
- Conducting airways
  - Generations 0 to 16
  - Trachea to terminal bronchioles
  - Includes bronchi and bronchioles
  - Airways ciliated
  - Contain bronchial smooth muscle
- Alveolated airways
  - Generations 17 to 23
  - Respiratory bronchioles to alveolar sacs

WEIBEL MODEL OF LUNG (2)

<table>
<thead>
<tr>
<th>Generation</th>
<th>Name</th>
<th>Number of Airways</th>
<th>Diam (cm)</th>
<th>Total cross-section (cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Trachea</td>
<td>1</td>
<td>1.8</td>
<td>2.54</td>
</tr>
<tr>
<td>1</td>
<td>Main bronchi</td>
<td>2</td>
<td>1.22</td>
<td>2.33</td>
</tr>
<tr>
<td>17</td>
<td>Respiratory bronchioles</td>
<td>131,072</td>
<td>0.054</td>
<td>300</td>
</tr>
<tr>
<td>23</td>
<td>Alveolar sacs</td>
<td>8,388,608</td>
<td>0.041</td>
<td>11,800</td>
</tr>
</tbody>
</table>

CROSS-SECTIONAL AREA OF UPPER Airways

CONDUCTING AIRWAYS
- Anatomic dead space approx. 150 mL in adults
- Airway narrowing in asthma and COPD
  - Smooth muscle bronchospasm
  - Airway inflammation
  - Mucus hypersecretion
- Sympathetic and parasympathetic nervous systems
  - Beta-adrenergic bronchodilators
  - Anticholinergic bronchodilators
- Mucociliary clearance
  - An essential lung defense mechanism
  - Deposited drug may be cleared from lungs
- Clearance abnormally slow in some diseases
  - e.g. cystic fibrosis, bronchiectasis

ALVEOLATED AIRWAYS
- Each alveolus 0.3 mm diameter, total > 100 million
- Alveoli form honeycomb around alveolar duct
  - Loss of elastic support when alveoli damaged
- Alveolar surface area
  - Mean 100 to 190 m²
- Drug absorption
  - Transcellular (through cells)
  - Paracellular (via tight junctions between cells)
  - Absorption rate of peptides inversely proportional to molecular weight
- Lung defense mechanism: alveolar macrophages
- Drug inactivation by esterases

PULMONARY AND SYSTEMIC CIRCULATIONS
From West, J.B., (2004), Respiratory Physiology, the Essentials

DISTRIBUTIONS OF BETA-2 RECEPTORS, MUSCARINIC M3 RECEPTORS AND AIRWAY SMOOTH MUSCLE IN HUMAN LUNG
From Howarth P.H., (2001), J. Aerosol Med. 14, Supplement 1, S27-S34

WALL OF A BRONCHUS

WALL OF THE ALVEOLATED AIRWAYS

PULMONARY CIRCULATION (ALVEOLI)
RA: Right atrium
RV: Right ventricle
LA: Left atrium
LV: Left ventricle

SYSTEMIC CIRCULATION (INCLUDING CONDUCTING AIRWAYS)

RA: Right atrium
RV: Right ventricle
LA: Left atrium
LV: Left ventricle

MUCUS
- Gel layer
- Sol layer

DEGONING LUNG
- Smooth muscle

CONDUCTING AIRWAYS
- Efferent bronchial nerve fibers
- Sympathetic nerve fibers
- Parasympathetic nerve fibers

BRONCHUS
- Epithelial cells
- Smooth muscle
- Cartilage

ALVEOLATED AIRWAYS
- Tight junctions
- Tight junctions
- Tight junctions
- Tight junctions
- Tight junctions

TRACHEA
- Bronchi
- Bronchioles
- Alveoli

RELATIVE DENSITY OF SMOOTH MUSCLE AND RECEPTORS

BETA-2 RECEPTORS
- Muscarinic M3 receptors
- Smooth muscle

PULMONARY VEIN
- VENACAVA

PULMONARY ARTERY
- AORTA

SYSTEMIC CIRCULATION (INCLUDING CONDUCTING AIRWAYS)
**AIRFLOW IN THE LUNGS**

- Diaphragm and intercostal muscles contract to expand the lungs.
- “Tidal” breathing
  - In adults: 500 mL at 15 breaths per minute
  - Young children: smaller volumes, higher breathing rates
  - “Duty cycle” slightly less than 0.5 in healthy subjects
- Slow deep breaths or rapid inhalation sometimes required when using inhaler devices
- Laminar versus turbulent flow
  - Airflow often turbulent in the first few generations
  - Reynolds number determines likelihood of turbulence

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**LUNG VOLUMES**

From West, J.B., (2004), Respiratory Physiology, the Essentials

- FRC: Functional residual capacity
- TV: Tidal volume
- TLC: Total lung capacity
- RV: Residual volume
- VC: Vital capacity
- IRV: Inspiratory reserve volume
- ERV: Expiratory reserve volume
- IC: Inspiratory capacity

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**FORCED VITAL CAPACITY MANEUVER**

- FEV1: Forced expiratory volume in 1 second
- FVC: Forced vital capacity

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**FEV1 AND FVC BEFORE AND AFTER A BRONCHODILATOR**

- FEV1: Forced expiratory volume in 1 second
- FVC: Forced vital capacity

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**LUNG FUNCTION TESTS: NORMAL VALUES**

- Normal predicted values of lung function parameters depend on sex, age, height, and ethnic group
- If FEV1 = 2L:
  - Highly abnormal in a young male
  - Normal in an elderly female
- Interpretation of spirometric data: reference to predicted values
- FEV1 and disease severity (ATS / ERS guidelines):
  - > 70 % predicted: Mild
  - 50 to 70 % predicted: Moderate / moderately severe
  - < 50 % predicted: Severe / very severe

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**SPIROMETRY: EXPIRATORY FLOW VOLUME CURVE**

- PEF: Peak exhaled flow rate
- Vmax50 and Vmax25: Forced expiratory flow rate when 50 % and 25 % of FVC remain to be exhaled
**ADVANTAGES OF PULMONARY ROUTE: LOCALLY ACTING DRUGS**

- Targeted delivery
  - Drug is deposited at its site of action
  - Systemic absorption and distribution throughout the body not required
  - Beneficial effects despite negligible systemic levels
  - Effectiveness not limited by poor absorption or hepatic first-pass metabolism

- Clinical advantages
  - Low dose compared to oral therapy
  - Low incidence of systemic side-effects
  - Rapid onset of drug action

**ADVANTAGES OF PULMONARY ROUTE: SYSTEMICALLY ACTING DRUGS**

- Many drugs are either not absorbed from the GI tract or have highly variable absorption
  - Parenteral delivery needed (usually subcutaneous injection)
  - Insulin is a well-known example
  - Patients may be unwilling to give themselves injections

- Pulmonary epithelium offers an alternate non-invasive injection-free portal of entry to the body
  - Large alveolar surface area
  - Thin barrier between air and blood in alveoli
  - Rapid onset of drug action
  - Pain control – migraine, post-operative, cancer

**COMPARATIVE INHALED AND ORAL DOSES OF BETA-2 RECEPTOR BRONCHODILATORS**

<table>
<thead>
<tr>
<th></th>
<th>Inhaled dose</th>
<th>Oral dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose, mg</strong></td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>pMDI dose</td>
<td>0.1</td>
<td>1</td>
</tr>
<tr>
<td>Oral dose</td>
<td>1.0</td>
<td>10</td>
</tr>
</tbody>
</table>

*From Gebbie, T., (1982), Steroids in Asthma*
LIMITATIONS OF THE PULMONARY ROUTE (2)

- Inhaler devices
  - Correct inhaler technique
  - Only some inhalers are suitable for delivering doses > 1 mg

- Lung defense mechanisms
  - Evolved to prevent entry of inhaled materials
  - To remove them once deposited
  - Successful inhaled drug delivery seeks to by-pass these defense mechanisms

PRESSURIZED METERED DOSE INHALERS (pMDIs)

- Press-and-breathe pMDI
- Autohaler®, image courtesy of 3M Pharmaceuticals
- Aerochamber®, image courtesy of Trudell Medical International
- Watchhaler®, image courtesy of Activaero

DRY POWDER INHALERS (DPIs)

- Spinhaler®, image courtesy of Vectura
- Clickhaler®, image courtesy of Vectura
- Turbuhaler®, image courtesy of AstraZeneca

NEBULIZERS AND EMERGING TECHNOLOGIES

- LC Sprint®, image courtesy of PARI
- 1-neb® AAD® System, image courtesy of Respironics
- AERx®, image courtesy of Aradigm

INHALER TECHNOLOGIES

- Roles for simple and complex devices
- More efficient and more reproducible drug delivery
- Wide range of dose sizes
- Inhaler selection
  - Patients willing to use inhaler
  - Patients able to use correctly

KEYS TO SUCCESS IN PULMONARY DRUG DELIVERY

- Effective and safe drug molecules, e.g. albuterol
- Well-designed inhaler devices and formulations
  - Correct particle size
- Education of health-care workers and patients
  - "10 % medicine and 90 % education"
  - Avoidance of "crucial" errors in inhaler technique
  - Adherence to (compliance with) treatment