Strategies in Cardiovascular Disease and Respiratory Disease

Drug Discovery and Medicinal Chemistry

Asthma

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Course Overview

Lecture 1:
• Overview of the human heart
• Cardiac agents used to treat
  • Heart failure, Angina and Cardiac arrhythmia

Lecture 2:
• Drugs targeting Adrenergic Receptors (GPCRs)

Lecture 3:
• Agents affecting the Renin-Angiotensin Pathway

Lecture 4:
• Overview of normal lung function
• Drugs for the management of asthma
Learning Objectives

• Explain how the lungs work and the pathogenesis of asthma.
• Give examples of each type of asthma treatment and their mode of action.
• Describe how the structure of key drugs relates to their biological activity.

Recommended Reading:
Asthma – A Brief History

- Asthma has been known since antiquity, the earliest reference is in Homer’s Iliad as a noun meaning breathlessness.
- The earliest use as a medical term comes from Hippocrates in Ancient Greece.
- There are currently around 5.4 million people suffering from asthma in the UK (1 in 11 people)
- In 2014 (most recent stats) 1216 people died from asthma in the UK.
- The NHS spends around £1 billion per year treating asthma.
The Lungs

- In order to understand asthma and the drugs used to treat it we need to understand how the lungs work.
Asthma is a chronic, complex, airway disorder characterised by airflow obstruction, bronchial hyperresponsiveness and inflammation.

Symptoms include difficulty breathing, wheezing and cough.

The most common form is caused by an allergic response to environmental allergens (pollen, dust mites, pet hair etc)

Aside from environmental triggers, an asthmatic attack can be triggered by infection, strenuous exercise, drugs and environmental pollutants.
Asthma Pathogenesis

- Alleens
- Lung epithelia
- Thymic Stromal Lymphopoietin (TSLP)
- Immunoglobulin-E (IgE)
- Interleukin-4 (IL-4)
- Mast cell
- Dendritic cells
- T<sub>FH</sub> cell
- B cell
- Activating & Degranulation
- Leukotriene
- Histamine
- Prostaglandin
Treatments

- The therapeutic management of asthma requires the use of quick acting drugs to relieve an acute attack as well as drugs to control symptoms long-term.

- Drugs are inhaled in aerosolised form administered using inhalers.

- Quick reliever medication is almost always an inhaled short-acting $\beta_2$-adrenergic agonist.

- Controller drugs are inhaled corticosteroids, long-acting $\beta_2$-adrenergic agonists, leukotriene modifiers, cromolyn sodium and/or methylxanthines.
β₂-Receptor Agonists

- β₂-receptors are found primarily in the lung.
- Agonists selective for the β₂-receptor subtype cause bronchial dilation, counteracting effects of bronchospasm seen in an asthma attack.
- Non-selective agonists, however, would have stimulatory cardiac effects so have limited use in cardiac patients.

Epinephrine

Isoproterenol
**β₂-Receptor Agonists**

- Epinephrine and isoproterenol were replaced with isoetharine.
- The α-ethyl group confers some β₂-selectivity although higher doses lead to β₁ cardiovascular effects.
- Metaproterenol is the resorcinol analogue of isoproterenol. The resorcinol enhances β₂-selectivity.
- Terbutaline is the $N\text{-}t\text{-}butyl$ analogue and has three-fold greater potency for β₂-receptors than metaproterenol.
β₂-Receptor Agonists - Salmeterol

- Salmeterol was one of the top 10 selling drugs in 2016.
- It has an N-phenylbutoxyhexyl, a β-hydroxyl and a salicyl ring which, in combination, give ultimate β₂-selectivity.
- Salmeterol has the highest receptor affinity of all adrenergic agonists.
- It is resistant to metabolism and lipophilic resulting in a prolonged mode of action (effects last 12 hours). Therefore used as a controller for long-term treatment.
β₂-Receptor Agonists - Formoterol

- Formoterol has a β-directing N-isopropyl-ρ-methyloxyphenyl group and a unique m-formamide which provides β₂-selectivity.
- Formoterol has a more rapid onset than salmeterol, due to increased water solubility. Moderate lipophilicity gives a long duration of action.
- There are two chiral centres. The R,R-enantiomer is 1000x more active than the S,S-enantiomer and is available as arformoterol as a treatment for COPD.
Methylxanthines

- Methylxanthines naturally occur in coffee (caffeine), and cacao (theobromine). The differ in the position and number of methyl groups on their xanthine ring.

- Theophylline is used to treat asthma due to its bronchodilating effects.
- It has a very narrow therapeutic index and requires close patient monitoring to avoid serious side effects.
Methylxanthines

- Theophylline inhibits the enzyme phosphodiesterase which hydrolyses cAMP in smooth muscle resulting in bronchodilation.
Steroids - Adrenocorticoids

- Adrenocorticoids are a class of steroid formed in the adrenal cortex (part of the adrenal gland above the kidney).
- They can be subdivided into glucocorticoids and mineralocorticoids.
- Glucocorticoids are so named as they affect glucose metabolism but they also have significant anti-inflammatory effects making them useful as asthma treatments.
Glucocorticoid Structure

- Methylation at C10 and C13 and an ethyl group at C17 gives a 21-carbon structure called a pregnane.
- All ring junctions are trans.
- All have a double bond in ring A, OHs at C11, C17 and C21 and 3- and 20-keto groups.
Steroid Pharmacologic Action

- Glucocorticoids have anti-inflammatory activity through affecting protein expression.
- They stimulate the synthesis of annexin (lipocortin) which inhibits the activity of the enzyme phospholipase A₂.
- Phospholipase A₂ causes the release of arachidonic acid which ultimately results in production of inflammatory prostaglandins and leukotrienes.
Steroid Mechanism of Action

- Glucocorticoids affect protein synthesis.
- Initially they bind to receptors inside the cell forming a complex which travels to the nucleus.
- The complex then binds DNA and affects the levels of gene transcription.
Steroid Mechanism of Action

- Glucocorticoids form a tight complex with their receptors, almost all of the atoms make contact with one or more amino acid residues.
Synthetic Steroids – Pro Drugs

- Despite the presence of hydroxyl groups glucocorticoids are lipophilic.
- The OH groups can be esterified to increase or decrease lipophilicity.
- C21 is most reactive followed by C17, C11 is too hindered to react.
- C21-OH must be free to H-bond to the receptor so esters are pro-drugs. C17-OH is needed for metabolism.
- If C16-OH is present ketals can provide additional increase in logP and increased duration of action.
Synthetic Steroids

- Beclomethasone dipropionate has an extra A ring double bond which increases activity 4-fold. The C16β-methyl group decreases competing mineralocorticoid activity, C9α-Cl increases both.

- Fluticasone propionate has a unique C20 thiofluoromethyl group. It has a 36-fold higher receptor affinity than beclomethasone.
Synthetic Steroids

- Mometasone furonate has a number of unique functional groups.
- The combination of the C21-chloro group and the C17-furoic ester results in the highest glucocorticoid receptor affinity.
- As with previous examples, the C16-methyl decreases mineralocorticoid activity giving increased selectivity and the C9-Cl enhances both glucocorticoid and mineralocorticoid activity.
The discovery that a herb Khella had mild bronchodilating effects led to the isolation of khellin.

Synthetic derivatives were prepared with no improvement in activity.

Dr Roger Altounyan noted, while experimenting on himself, that if one analogue was inhaled before an attack it gave excellent protection against its severity.

This ultimately led to the discovery of cromolyn sodium (US)/sodium cromoglycate (EU).
Mast Cell Degranulation Inhibitors

• Sodium cromoglycate interacts with sensitised mast cells before the antigens.

• This inhibits the degranulation process preventing the release of histamine, leukotrienes and prostaglandins.

• The structure contains the core benzopyrone of khellin. The rings are essential for activity and must be coplanar.

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\text{Sodium Cromoglycate}
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Leukotriene Modifiers

- Leukotrienes are inflammatory mediators released by mast cells and have bronchoconstrictive activity.
- Inhibitors of their biosynthesis and antagonists of their receptors have been developed.
- Zileuton inhibits 5-lipogenase, a key enzyme in leukotriene biosynthesis.
- Both enantiomers are pharmacologically active.
- The N-hydroxy group is essential for activity and the benzothienyl adds lipophilicity.
- Zileuton also increases serum levels of the drug propranolol.
Leukotriene Modifiers

- The search for leukotriene receptor antagonists used a combination of structure analogues and screening.
- It was found that the lipophilic tail could be mimicked with a variety of aromatic rings, the thioester could be replaced with an alkyl carboxylic acid and the C1 carboxylate had to be retained.
- Montelukast is a high-affinity, selective antagonist of the cysLT$_1$ receptor.
- It interacts with three hydrophobic regions and one basic lysine.
Summary

- Asthma is a chronic airway disorder which causes difficulty breathing and affects millions of people worldwide.
- Treatments are usually aerosolised and are usually adrenergic receptor agonists, corticosteroids, methylxanthines, cromolyn sodium and/or leukotriene modifiers.
- $\beta_2$-receptor agonists cause bronchial dilation and are based on the structure of the natural ligand epinephrine.
- Glucocorticoids have a specific 3D structure allowing them to alter protein expression levels, leading to downstream anti-inflammatory effects.