Strategies in Cardiovascular Disease and Respiratory Disease

Drug Discovery and Medicinal Chemistry

Cardiac Agents
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

• Understand how the heart pumps blood around the body and the action potential generated by the conduction system.
• Describe the three types of heart disease and give examples of how to treat them.
• Describe the structural features and mode of action of cardiac glycosides and organic nitrates.
• Give examples of each class of ion channel blocker and explain their effect on conduction.

Recommended Reading:
In order to understand how drug molecules act on the heart we need to understand how it works.
The Heart

- In order to understand how drug molecules act on the heart we need to understand how it works.

Right atrium contracts to pump blood through into the right ventricle

Left atrium contracts to pump blood through into the left ventricle

- Superior vena cava
- Right pulmonary veins
- Right atrium
- Right ventricle
- Inferior vena cava
- Aorta
- Pulmonary artery
- Left atrium
- Left pulmonary veins
- Left ventricle
- Septum
In order to understand how drug molecules act on the heart we need to understand how it works.

- Right ventricle contracts, deoxygenated blood travels to the lungs
- Left ventricle contracts, oxygenated blood around the body
In order to understand how drug molecules act on the heart we need to understand how it works.

These structures form the conduction system of the heart:

- The SA node is the natural pacemaker and initiates the cardiac cycle.
- After a delay signal transmits to the AV node.
- Distal to the AV node is the Bundle of His.
- Signal is sent to the cardiac muscle by Purkinje fibres.

Diagram:

- Sinoatrial (SA) Node
- Atrioventricular (AV) Node
- Bundle of His
- Purkinje Fibres
Cardiac Agents

- Cardiac agents are drugs which treat heart disease

- Heart disease can be grouped into three main disorders
  - Cardiac failure or contractile dysfunction (heart failure)
  - Ischemic heart disease (angina)
  - Cardiac arrhythmia
Heart Failure

- Cardiac failure or (congested) heart failure is the inability of the heart to pump blood at a rate required by metabolising tissues.
- Direct result of reduced contractility of cardiac muscles, especially in the ventricles.
- Overall – decreased cardiac output and increased blood volume in the heart (hence congested).

- Common causes include heart attacks and high blood pressure
Heart Failure

• Cardiac failure or (congested) heart failure is the inability of the heart to pump blood at a rate required by metabolising tissues.
Cardiac Glycosides

- Treatment for heart failure often includes elements of lifestyle change.
  - Controlling diet/exercise
  - Stopping smoking

- Medication is also very common in order to reduce and slow down the effects of the disease.
Cardiac Glycosides

• Naturally occurring drugs found as metabolites in plants such as foxgloves.
• Used as treatments and poisons(!) since 1500BC.
• They are glycosides; a sugar (glycone) bonded to a non-sugar (aglycone)
• The aglycone is a steroid moiety based on a steroid nucleus with a unique ring structure.

Steroid nucleus = Tetracyclic cyclopentanoperhydrophenanthrene
Cardiac Glycosides - Aglycone

- Unique ring structure makes them distinguishable from other steroid structures.
- Rings A-B and C-D are *cis* fused whereas rings B-C are *trans*. This gives a characteristic U-shape.
- In most cases there are CH$_3$ groups at C-10 and C-13.
- Hydroxyl groups are at C-3 (the site of sugar attachment) and C-14.
Cardiac Glycosides - Aglycone

- Additional hydroxyls are often found at C-12 and C-16 this gives rise to structural variation.
- The lactone at C-17 is another major source of variation – most of plant origin possess a five membered α,β-unsaturated lactone.

Digitoxigenin

Digoxigenin

Gitoxigenin
Cardiac Glycosides – Sugar

- The hydroxyl at C-3 is conjugated to either monosaccharide or polysaccharides via β-1,4-glycosidic bonds.
- Number and identity of the sugars varies throughout the glycoside family.

β-D-Digitoxose
β-D-Glucose
β-D-Cymarose
Digitoxin and Digoxin

Digitoxin

\[
\text{P} = 96.5 \\
\text{Half-life} = 5-7\text{days}
\]

Digoxin

\[
\text{P} = 81.5 \\
\text{Half-life} = 1-2\text{days}
\]
Mode of Action and SAR

• Cardiac glycosides act directly on cardiac muscle and the conduction system (the SA node, the AV node and the His-Purkinje system).
• Possible target is an enzyme (Na⁺/K⁺-ATPase) which provides energy to fuel changes in the action potential responsible for contraction.
• This results in changes in the electrophysiology of the heart including contractility, conductivity and refractory period.
• 17-lactone hypothesised to play an important role in receptor binding – carbonyl oxygen may play an important role.
• Steroid structure is also important, a cis C-D ring is critical.
Angina pectoris affects the coronary arteries which supply oxygenated blood to all heart tissues.

When the lumen of the coronary artery becomes restricted less blood (and therefore oxygen) is supplied to the heart.

Heart is said to be ischemic (oxygen deficient).

Angina is the primary symptom of ischemic heart disease.
Organic Nitrates

- Organic nitrates have been the primary method of angina treatment over the last 100 years.
- They are esters formed from organic alcohols and nitric acid.
- Antianginal effect of amyl nitrite was discovered in 1857.
- Many other organic nitrates are in clinical use today.
Organic Nitrates – Mode of Action

- Organic nitrates are vasodilating.
- Effect on the veins reduces venous return to the heart (decreased preload).
- Effect on the coronary artery decreases the resistance of peripheral tissues (decreased afterload).
- Overall decrease in the workload of the heart.
- Organic nitrates are a source of nitric oxide (NO) which increases intracellular cGMP concentration which, in turn, blocks vascular contractions.

\[ \text{NO} \]

Cardiac Arrhythmia

• Arrhythmia is an alteration in the normal electrical impulse rhythm that leads to contraction of the heart.
• Rates below normal = sinus bradycardia, rates above = sinus tachycardia.
• Irregular cardiac rhythms can occur due to abnormal SA node activity, other sites release electrical signals (ectopic arrhythmia) or signal re-entry.
• Four classes of drugs; Na\(^+\) channel blockers, β-blockers (lecture 2), K\(^+\) channel blockers and Ca\(^{2+}\) channel blockers.
Cardiac Arrhythmia

• Reminder of the electrical impulse rhythm.

• The SA node is the natural pacemaker and initiates the cardiac cycle.

• After a delay signal transmits to the AV node.

• Distal to the AV node is the Bundle of His.

• Signal is sent to the cardiac muscle by Purkinje fibres.
Cardiac Arrhythmia

- Normal physiological action potential.

**Phase 0:** Rapid depolarisation, permeability for Na⁺ ions increases, Na⁺ enter the cell.
Cardiac Arrhythmia

- Normal physiological action potential.

**Phase 1:** Ionic shift, reduced Na\(^+\) ion entry, influx of Ca\(^{2+}\) and efflux of K\(^+\) ions.
Cardiac Arrhythmia

- Normal physiological action potential.

**Phase 2:** Plateau phase, slow influx of Ca^{2+} triggered by rapid Na^{+} entry in phase 0, K^{+} efflux.
Cardiac Arrhythmia

- Normal physiological action potential.

Phase 3: Restoration of membrane potential, slowing of Ca^{2+} influx, K^{+} efflux.
Cardiac Arrhythmia

- Normal physiological action potential.

Phase 4: Resting phase, ion pumps restore ions to proper local concentrations.
Sodium Channel Blockers

- Class I antiarrhythmiac drugs are Na\(^+\) channel blockers.
- Class IA slow phase 0 of action potential.
- Quinidine is widely used to treat arrhythmia.

![Quinidine structure]

- Built from a quinoline ring and a bicyclic quinuclidine ring – two basic Ns.
- Quinuclidine N has the higher pK\(_a\).
**Sodium Channel Blockers**

- Class I antiarrhythmic drugs are Na\(^+\) channel blockers.
- Class IB shorten phase 3 repolarisation.

Phenytoin

- Used to treat seizures but found to be beneficial for arrhythmias.
- Metabolised to p-hydroxylated derivatives

- Class IC slow phase 0 but with slow rates of dissociation from the channel.

Flecainide
Potassium Channel Blockers

- Class III antiarrhythmic drugs are K⁺ channel blockers.
- They cause homogeneous prolongation of the duration of action potential by blocking most K⁺ channels.

**Amiodarone**

- Used only in life threatening cases due to severe side effects and toxicity.
- Acts on the lipid membrane to alter ion channel and receptor activity.
Potassium Channel Blockers

- Class III antiarrhythmic drugs are K⁺ channel blockers.

- They cause homogeneous prolongation of the duration of action potential by blocking most K⁺ channels.

![Dronedarone (Multaq) molecule]

- Additional methylsulfonamide reduces lipophilicity and neurotoxic effects. Iodine groups removed to reduce organ toxicity.
Calcium Channel Blockers

- Class IV antiarrhythmic drugs are Ca\(^{2+}\) channel blockers.
- Selectively block the inward current carried by Ca\(^{2+}\) ions – shown to be important for normal action potential in SA node cells.

![Verapamil](attachment:image.png)

- S enantiomer is one order of magnitude more potent than the R enantiomer.
Summary

• Heart disease can be grouped into three main disorders.
• Cardiac glycosides are composed of glycone and aglycone moieties.
  • They act directly on heart muscle to treat heart failure.
  • Their steroid structure is key to activity.
• Organic nitrates are used to treat angina
  • By producing nitric oxide they block vascular contractions.
• Cardiac arrhythmia is an alteration in normal heart rhythm.
  • It can be treated by four different types of ion channel blockers.