Strategies in Cardiovascular Disease and Respiratory Disease

Drug Discovery and Medicinal Chemistry

Adrenergic Receptors

Dr Anna Barnard - Spring 2017
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

• Describe the different classes of adrenergic receptor GPCR and their downstream biological effect.
• Discuss, with examples, the development of selective antagonists.
• Explain how alteration to example drug structures change their activity.
• Discuss the effect of stereochemistry on the activity and administration of selected examples.

Recommended Reading:
GPCRs

- G-protein coupled receptors (GPCRs) are the largest family of membrane proteins encoded by the human genome.
- They communicate signals from the extracellular environment inside the cell in response to a variety of stimuli – light, proteins, peptides, small molecules, hormones and ions.
- GPCRs interact with G protein partners inside the cell triggering a cascade of responses.
- One of the top 10 selling drugs in 2016 is Salmeterol (Lecture 4) which targets a GPCR. Sales of $5 billion!
Adrenergic Receptors

- Adrenergic receptors are GPCRs which respond to epinephrine and norepinephrine and are drug targets for both cardiac and asthma drugs.

![Chemical structures of Epinephrine and Norepinephrine](image)

- Epinephrine and norepinephrine are catecholamines.
- They generally result in a ‘fight-or-flight’ response which can include increased rate and force of heart contraction, rise in blood pressure or shift of blood flow to skeletal muscles.
Receptor Types

- In 1948 Raymond Ahlquist classified epinephrine receptors as either α or β according to their response to agonists.
- Further sub-classification of the receptors into α₁ and α₂, β₁, β₂ and β₃.

Diagram showing α₁ and β receptors with Gq and Gs proteins, leading to Phospholipase C and Adenylyl cyclase, respectively.
Receptor Types – $\alpha_1$

- $\alpha_1$ receptors are linked, through $G$ protein $q$, to the hydrolysis of phosphatidylinositol-4,5-biphosphate.

![Diagram showing the interaction of $\alpha_1$ receptors with $G_q$, leading to the hydrolysis of phosphatidylinositol-4,5-biphosphate (PIP) into inositol-1,4,5-triphosphate (IP$_3$) and 1,2-diacylglycerol (DAG).]
β receptors are linked, through G protein $s$, to the formation of cyclic adenosine monophosphate (cAMP).
**Therapeutic Significance**

- Drugs targeting different classes of adrenergic receptors can be used to treat a number of conditions.
- These receptors are also found in the eye, liver, uterus and intestine.

<table>
<thead>
<tr>
<th>Organ/Tissue</th>
<th>Receptor Type</th>
<th>Response</th>
<th>Drug Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterioles</td>
<td>$\alpha_1$</td>
<td>Constriction</td>
<td>Antagonist</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>$\beta_2$</td>
<td>Dilation</td>
<td>Agonist</td>
</tr>
<tr>
<td>Heart</td>
<td>$\beta_1$</td>
<td>Increased force and rate</td>
<td>Antagonist</td>
</tr>
<tr>
<td>Lungs</td>
<td>$\beta_2$</td>
<td>Relaxation (bronchodilation)</td>
<td>Agonist</td>
</tr>
</tbody>
</table>
**α-Receptor Antagonists**

- α antagonists can be used to treat hypertension (high blood pressure).
- Phenoxybenzamide (Dibenzyline) is a β-haloalkylamine that alkylates α-receptors.
- Administered as an acid salt but equilibrium with the free base creates a nucleophile. Aziridinium reacts with nucleophilic amino acids (Cys, Lys, Ser).

![Chemical Structures](image)
Selective $\alpha_1$-Receptor Antagonists

- Prazosin was the first $\alpha_1$-selective blocker and was discovered in the late 1960s.
- Two others have since been developed, along with related compounds targeting prostate gland receptors.
Selective $\alpha_1$-Receptor Antagonists

- All have 4-amino-6,7-dimethoxyquinazoline ring systems attached to a piperidine.
- Reduction of the furan to a THF increases duration of action by altering rate of metabolism (6 vs 18 hours).

Prazosin (Minipres)

Terazosin (Hytrin)

Doxazosin (Cardura)
β-Receptor Antagonists

• In the 1950s dichloroisoproterenol was discovered to be a β-antagonist.
• Replacement of the 3,4-dichloro substituents to form a naphthyl afforded pronethalol.
• Pronethalol was introduced in 1962 but was withdrawn in 1963 due to tumour induction in animal tests.
β-Receptor Antagonists

- It was then discovered that an oxymethylene bridge could be inserted into the arylethanolamine to afford propranolol.

![Pronethalol](image)

- Lengthening the side chain may seem to position binding groups in a non-optimal position.

- Molecular models have shown that the side chains can adopt a conformation placing the OH and NH groups in approximately the same position.
Stereochemistry Aside

- The R isomer is more effective isomer of pronethalol.
- However the S isomer more effective for propranolol.

- The S isomer is 130 times more potent than the R isomer of propranolol.
- Despite the differences in activity between the enantiomers of propranolol it is marketed as a racemic mixture.
Since the development of propranolol a large number of additional β-blockers have been brought to market.

- Propranolol
- Nadolol
- Penbutolol
- Pindolol
- Sotalol
- Timolol
$\beta_1$-Receptor Antagonists

- As propanolol became more widely used, a new series of 4-substituted phenyloxypropanolamines emerged which selectively inhibited cardiac stimulation.
- This led to the recognition that not all $\beta$-receptors were the same, and the introduction of $\beta_1$ and $\beta_2$ nomenclature.
**β₁-Receptor Antagonists - Esmolol**

- Esmolol is β₁-selective antagonist and is a methyl ester.

![Esmolol molecule]

- This makes it susceptible to hydrolysis by esterase enzymes. The acid metabolite is inactive and readily excreted.

- Esmolol has a half-life of 8 minutes and is used when a short-acting antagonist is needed e.g. during surgery.
**β₁-Receptor Antagonists - Nebivolol**

- Nebivolol is β₁-selective antagonist with multiple chiral centres.

![Nebivolol structure](image)

- The *SRRR* isomer acts as a β-blocker and the *RSSS* isomer has a nitric oxide potentiating effect.
- Nitric oxide increases cGMP which leads to vasodilation.
- Nebivolol is therefore administered as a racemic mixture to take advantage of both pathways.
Summary

• GPCRs are important drug targets for many diseases including cardiovascular and respiratory diseases.
• $\alpha_1$ receptors in the arterioles and $\beta_2$ receptors in the lungs can be targeted to treat cardiovascular disease.
• Initially $\alpha$ and $\beta$-antagonists were developed before selective $\alpha_1$ and $\beta_2$ antagonists with $\beta$-blockers being commonly based on the structure of the natural ligand epinephrine.
• All $\beta$-blockers are chiral, which, in some cases effects their biological activity.