Anti-hypertensive agents

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Anti-hypertensive agents

- Angiotensin converting enzyme inhibitors (ACE inhibitors)
- Calcium channel blockers
- Adrenergic inhibitors:
  - Catecholamine storage and release inhibitors: Reserpine and guanethidine.
  - $\beta$-blockers: Propranolol.
  - $\alpha_1$-receptor antagonist: Pentazocin.
- Direct acting vasodilator: Hydralazine and sodium nitroprusside.
- Angiotensin II receptor antagonists: Losartan.
Angiotensin converting enzyme inhibitors
(ACE inhibitors)
**Role of ACE and Mechanism of action of ACE inhibitors**

Reduced blood pressure

lowered sodium excretion

Renin release from kidneys (Renin is an aspartate protease enzyme)

Formation of angiotensin I from angiotensinogen

ACE inhibitors

A polypeptide

Angiotensin II

Angiotensin III

Inactive product

Prostaglandin release

Vasodilation

Vasoconstriction

Aldosterone secretion

Increased peripheral resistance

Sodium and fluid retention

Increased blood pressure

ACE inhibitors will **decrease** blood pressure

1. Inhibiting the formation of Angiotensin II
2. Inhibiting the metabolism of Bradykinin
Enzyme called **RENNIN** is released from the kidney into the blood

Rennin catalyses the breakdown of **ANGIOTENSINOGEN** protein into an inactive **decapeptide** called **ANGIOTENSIN-I**

**ACE** catalyses the **hydrolysis of a dipeptide** fragment (**histidyl-leucine**) from the **C-terminal** to form the **octapeptide** **ANGIOTENSIN-II**

**ACE** is a **zinc-containing peptidase** purified in 1956 and is the member of a group of enzymes called **zinc metalloprotease**

**ACE active site:**

- Two hydrophobic pocket S1 and S1’
- A positively charged region (Arg145).
- Positively charged Zinc
**ANGIOTENSIN-II** is an important hormone that causes constriction of blood vessels, resulting in a rise in blood pressure.

**ACE inhibitors** are potential antihypertensive agents because they inhibit the production of angiotensin-II

![Angiotensin-Hormone-Diagram]

- **ANGIOTENSINOGEN**
- **RENIN**
- **ANGIOTENSIN-I**
- **ACE**
- **ANGIOTENSIN-II**

*(Vasoconstrictor)*

<table>
<thead>
<tr>
<th>Angiotensin I</th>
<th>Angiotensin II</th>
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<tbody>
<tr>
<td>Asp-Arg-Val-Tyr-Ile-His-Pro-Phe</td>
<td>Asp-Arg-Val-Tyr-Ile-His-Pro-Phe + His-Leu</td>
</tr>
</tbody>
</table>
ANGIOTENSINOGEN

RENIN

ANGIOTENSIN-I

ACE

ANGIOTENSIN-II (Vasoconstrictor)
ACE inhibitors

- Succinyl proline shown to be a selective but weak ACE inhibitor
- It was assumed that there would be two pockets available to accommodate amino acid side chains (pocket S1 and S1’)
- Methyl substituent was added to form additional hydrophobic interactions with S1’ pocket - extension strategy

\[
\text{Succinyl proline; } IC_{50} 628 \ \mu M
\]

\[
\text{SQ13 297; } IC_{50} 52 \ \mu M
\]
It was believed that the interaction between the Zinc atom in the enzyme and the carboxyl group in the carboxyalkanoyl moiety was important.

Improving this interaction was achieved by replacing the carboxyl group with a methylthiol group.

CAPTOPRIL

Thiol acts as bio-isostere for carboxylate ion.

Thiol group forms stronger interactions with the zinc ion because sulphur has greater affinity for Zinc than oxygen.

Potency increased one thousand-fold.

Captopril was the first non-peptide ACE inhibitor to be marketed.
CAPTOPRIL: Binding interactions

- Ionic interactions (02)
  - thiol group (SH) and zinc ion
  - carboxylate group and arginine (Arg145)
- Hydrophobic interactions
  - methyl substituent & S1’ pocket

Disadvantages of captopril

- The -SH group was found to cause unwanted side effects (agranulocytosis, skin rashes, loss of taste)
- It has short half-life that necessitates two or three times per day dosing, reducing patient compliance
- Replacement of thiol group back with carboxylate group likely to decrease side effects, but lead to a drop in activity
Replacement of thiol group back with carboxylate group likely to decrease side effects, but lead to a drop in activity

Need to introduce further binding interactions to compensate

Design of Enalaprilate

Carboxylate ion acts as zinc binding group

BUT weaker interaction than a thiol group

Compensated by extra binding interactions involving phenethyl, amine and methyl groups

Methyl group fits S1’ pocket

Phenethyl group fits S1 pocket

Amine introduced to mimic binding interactions of amide NH in substrate
Disadvantage of Enalaprilate

- It shows poor oral absorption due to the presence of 2 carboxylic acid (COOH) groups which undergoes ionisation in the gut.

Design of Enalapril

- Enalapril is the prodrug of enalaprilate where the carboxylic acid group was masked by conversion to the ethylester.

- It has improved oral activity and absorb well from the gut before undergoing hydrolysis back to the active enalaprilate.

- It may not be a good choice of drug for patients with hepatic insufficiency.
LISINOPRIL

- Similar to Enalaprilate
- Methyl group has been extended to mimic side chain of lysine

- Crystal structure of lisinopril with ACE was solved in 2003
- Demonstrates that a lysine residue is involved in the ionic bond to ACE
- **LISINOPRIL** well absorbed in the gut yet **ENALAPRIT** was not
- Appears that the lysine residue in **LISINOPRIL** permits peptide-mediated transport from the gut to the portal circulation
- **NO enzymatic hydrolysis is required** like enalapril prodrug
- So less likelihood of problems for patients with hepatic insufficiently (i.e. older patients)
The main SAR for ACE inhibitors:

- A **zinc coordinating group** (carboxylate anion or any other negatively charged species).
- A carboxylate group to form ionic interaction with the arginin in the active site.
- A **6-7 atom distance** between the carboxylate and the zinc coordinating group.
- **Hydrophobic groups** to interact with the two hydrophobic pockets.
ACE inhibitors common S/E

- Vasodilator edema
- Persistent dry cough
- Headache
- Dizziness
- Fatigue
- Nausea
- Renal impairment
- Might increase inflammation-related pain (Due to accumulation of pradykinin)
Calcium channel blockers (CCB)

- Calcium plays a major role in the regulation of many cellular processes, mainly in muscle contraction.
- The entry of extracellular Ca\(^{++}\) into the smooth muscle cytosol and their release from the intracellular storage sites is very important for the initiation of muscle contraction and vasoconstriction as well as high blood pressure.
- Calcium channel blockers will interfere with the entrance of calcium into the cytosol resulting in vasodilatation and reduce blood pressure.
The majority of calcium channel blockers are 1,4-dihydropyridine derivatives. They act mainly on the L-type calcium channel (L for long lasting effect) after binding they cause conformational changes that affect Ca\(^{++}\) movement.
Calcium channel blockers

- No clear SAR for these agents.
- The difference in their structure will **mainly affect the pharmacokinetic profile not the activity** or the binding to the calcium channel.
Calcium channel blockers

- The general metabolism for CCB:

  Nefidipine

<table>
<thead>
<tr>
<th>Lactone metabolite (inactive)</th>
<th>Lactonization</th>
<th>COOH</th>
<th>OH</th>
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  Inactive
Direct acting vasodilators

**Hydralazine:**
- Reduces arteriole peripheral resistance.
- Interferes with calcium transport and activate guanylate cyclase and increases level of cGMP resulting into vasodilatation.

**Metabolism:**

![Chemical structure diagram showing the metabolism of Hydralazine](image)
Novel anti-hypertensive agents

Angiotensin II receptors Blockers

Angiotensinogen → Angiotensin I → Angiotensin II

- Renin
- ACE

ARBs

AT₁ receptor

AT₂ receptor
Novel mechanism of action is blocking angiotensin II receptors

Prevent the binding of angiotensin II to its receptor ($AT_1$) and hence prevent vasoconstriction.

They are competitive inhibitor for the receptor.

The prototype is losartan
Losartan Metabolism

- It is metabolized into an active metabolite: the carboxylic acid metabolite:

Losartan

Active
10X more active than losartan

Inactive

Minor Inactive
Valsartan (Diovan)

- Valsartan is a new anti-hypertensive agent with the same mechanism as losartan.

- The difference in structure between losartan and valsartan is:
  - Valsartan is more polar and has high volume of distribution.
  - Valsartan is a valine containing drug.
  - It will be in zwitter ionic form and this reduces its oral absorption.
Candesartan (Blopress®, Atacand®)

- Recent studies revealed that candesartan can reduce the risk of developing hypertension by two thirds.
- Used for treating hypertension mainly in combination with thiazide diuretics.
- Candesartan can be used in combination with an ACEIs.
- It is used as an alternative in patients intolerant of ACE inhibitor therapy.
- Given orally as cilexetil ester prodrug.
Telmisartan (Micardis®)

- Has the **longest duration of action** ($t_{1/2} = 24$ hr) and the **largest volume of distribution** among all angiotensin II receptor blockers.
- More lipophilic than other derivatives and high protein binding (>99.5%).

![Chemical structures of Telmisartan and its metabolite](image)
Thank you......... 😊