Learning Objectives

1. Explain the physiological role of the RAAS.
2. Describe the mechanisms of action for a range of drugs acting on RAAS and relate them to previous Drug Target/Mechanisms of Drug Action lecture.
3. Explain the therapeutic and adverse effects of drugs acting on the RAAS.

RAAS - Why do we care?
- Works synergistically with SNS
- Critical for controlling blood pressure
- Achieved via 2 main processes:
  1. Alteration of vascular tone
  2. Controlling natriuresis
- RAAS activation results in decreased space for blood to exist in and increased blood volume;

SNS is the counterbalance for the PNS covered in Drug Targets lectures.
**RAAS - Why do we care?**

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  ➤ Blood pressure

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**Main Components of the RAAS**

- **Renin** is a proteolytic enzyme produced in the juxtaglomerular cells.
- Released in response to sympathetic stimulation.
- Catalyses conversion of angiotensinogen into angiotensin I

\[
\text{angiotensinogen} \xrightarrow{\text{renin}} \text{angiotensin I}
\]

Renin is the foundation of the whole system

While the RAAS works synergistically with the SNS, it is also stimulated by SNS.

Angiotensin I has very little activity however it serves as an important precursor

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**Main Components of the RAAS**

\[
\text{angiotensin I} \xrightarrow{\text{ACE}} \text{angiotensin II}
\]

- Reaction involves cleaving off 2 amino acids
- ACE located primarily in endothelial cells in a variety of locations around the body
- Angiotensin II is a potent vasconstrictor via AT-1 receptors.

Ang II also has other effects mediated through AT-1
Smooth Muscle Contraction

CONTRACTION

- Agonists: Noradrenaline, Histamine, Angiotensin etc.
- Calcium channel blockers
- ATP
- Ca²⁺, Na⁺
- K⁺
- PLC
- Ca²⁺ release
- DEPOLARISATION

RELAXATION

- Potassium-channel activators (cromakalin etc.)
- Agonists: Adenosine, β-Agonists, Prostaglandins etc.
- AMP
- NO
- GMP
- GC
- PDE inhibitors
- Hyperpolarisation
- CONTRACTION

SMOOTH MUSCLE CELL


Renin – Angiotensin II

Control of renin release and formation, and action of angiotensin II.
Beyond Angiotensin II

- Angiotensin II can be further cleaved into angiotensin III and IV
- Ang III promotes aldosterone secretion (sodium reabsorption, thirst)
- Ang IV binds own distinct receptors to cause effects, including inhibition of clot clearance
  - Ang II is the main effector of the RAAS

Ang IV inhibits clot clearance by promoting the release of plasminogen activating inhibitor 1

Serial Cleavage of Angiotensinogen

Factors causing release include high K+ levels in blood and AT-1 activation (Ang II and III)
Receptors are steroid receptors - where in the cell are they likely to be found?

Aldosterone

- Released in response to a variety of factors
- Binds aldosterone receptors in collecting tubule
- Increases apical Na⁺ channels and basolateral Na⁺ /K⁺ transporters (3:2)
Activity – Identify drug targets

Control of renin release and formation, and action of angiotensin II. The vascular system. Rang, HP, MB BS MA DPhil Hon FBPharmacolS FMedSci FRS, Rang & Dale’s Pharmacology, 22, 265-284
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Drugs Targeting the RAAS

- ACE inhibitors (ACE-I)
- Angiotensin receptor antagonists (ARBs)
- Aldosterone antagonists
- Calcium channel blockers
- Diuretics
- Beta-blockers

Angiotensin Converting Enzyme Inhibitors (ACE-Is)

- Name says it all
- Mimic section of angiotensin I that binds to ACE
- Decreased Ang II levels
- e.g. cilazapril

\[
\text{angiotensin I} \xrightarrow{\text{ACE}} \text{angiotensin II}
\]

Dual Effect of ACE-Is

- ACE = kininase II
- Responsible for degrading bradykinin,
- therefore ACE-Is increase bradykinin
- Responsible for two main adverse effects
  1. Dry cough
  2. Angioedema
**ACE-I Induced Angioedema**

- Most commonly affecting lips, larynx and pharynx
- Frequency = 0.1-0.2%
- ACE-Is result in higher levels of bradykinin → vasodilation and increased permeability
- Cease medication, supportive care, bradykinin-specific treatment

Angioedema is abnormal swelling and inflammation
ACE-I medication can be replaced by ARB or CCB.
Bradykinin-specific treatment may decrease production of bradykinin or be a bradykinin receptor antagonist

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**Angiotensin Receptor Antagonists/Blockers (ARBs)**

- Competitive antagonists at AT-1 receptors
- Blocks most activity of the RAAS
- e.g. losartan

**ACE-I, ARB or Both?**

- Both ACE-Is and ARBs decrease likelihood of some cardiovascular events
- ACE-Is generally more effective, but more likely to display adverse effects
- ARBs possible as substitute
- Combination can be dangerous

ARBs have questionable efficacy in some conditions that are addressed by ACE-Is. Combination therapy has demonstrated increased risk of hyperkalemia and acute kidney injury
Aldosterone Antagonists

- e.g. spironolactone
- Antagonist at mineralocorticoid receptor
- Inhibits Na⁺ reabsorption caused by aldosterone

Calcium Channel Blockers

- Calcium channels are particularly important in muscle excitation and contraction
- Block channels inhibits smooth muscle contraction
- Decreased vasoconstriction
- Decreased blood pressure
- e.g. verapamil, nifedipine

Smooth Muscle Contraction
Calcium Channel Blockers

- Calcium channels are particularly important in muscle excitation and contraction
- Block channels inhibits smooth muscle contraction
  - decreased vasoconstriction
  - decreased blood pressure
- e.g. verapamil, nifedipine

Diuretics

- Ang II serves to promote retention of sodium and water. ∴ diuretics will oppose this action
- Primarily serve to increase excretion of sodium
- Variety of targets within the renal tubules
- Amiloride particularly relevant in counteracting RAAS activity

Loop diuretics, thiazides and amiloride all reduce sodium reabsorption and therefore water remains in tubules. Osmotic diuretics increase osmolarity of filtrate.
Beta Blockers

- Main action on SNS, but this interacts with RAAS
- Competitive antagonists at β-adrenergic receptors, primarily β₁
- Decrease cardiac contractility, decrease renin secretion
- e.g. metoprolol

Summary

- RAAS involved in regulation of blood pressure
- Pathology of RAAS involved in cardiovascular diseases
- Drugs exist that act on a variety of targets, including enzymes, receptors (GPCRs and steroid) and ion channels