The Renin-Angiotensin-Aldosterone System in hypertension and CHF

Block 18a

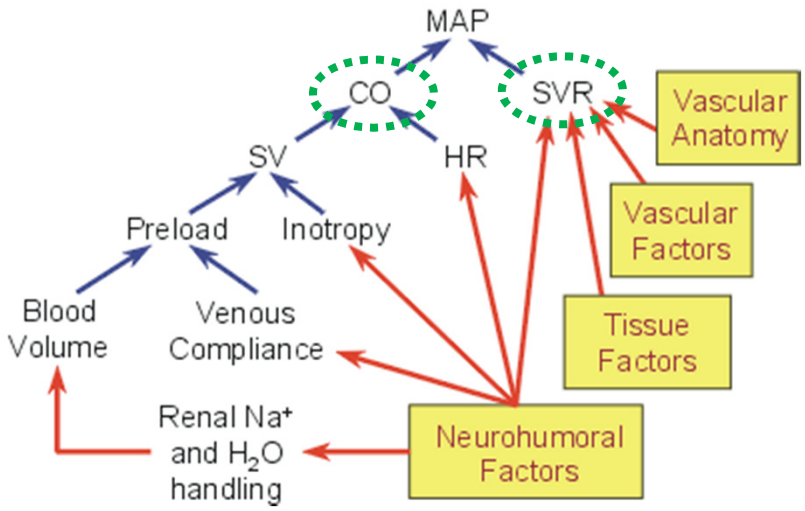
JJ van Tonder

Hypertension

- Blood pressure (BP) is directly proportionate to cardiac output (CO) and periferial vascular resistance (PVR)

BP = CO x PVR

Hypertension



Hypertension

- Why is it necessary to treat hypertension?

- Stroke
- Myocardial infarction
- Congestive heart failure
- Impaired kidney function – renal failure

Peripheral vascular resistance

Regulation of vascular smooth muscle

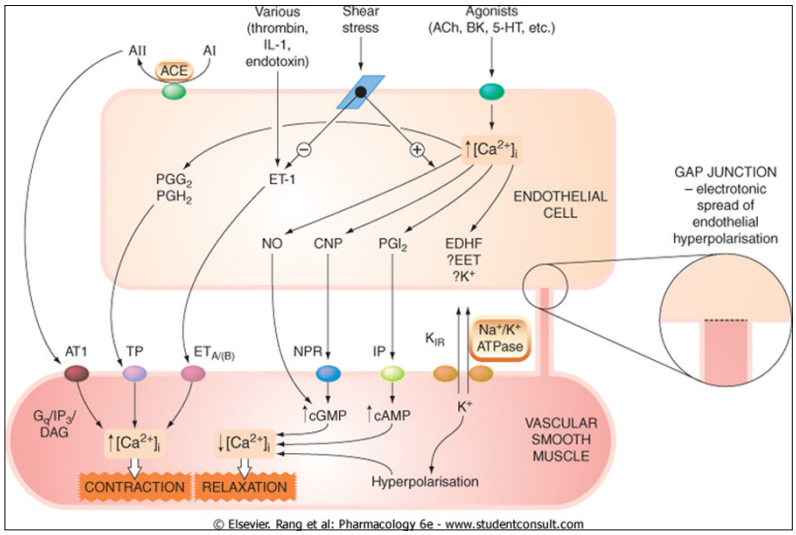
- Contraction - ↑Ca^{2+} (↑BP)
  - Angiotensin receptor I
  - Endothelin A/B receptors

  } Acts via G_q, IP_3, DAG

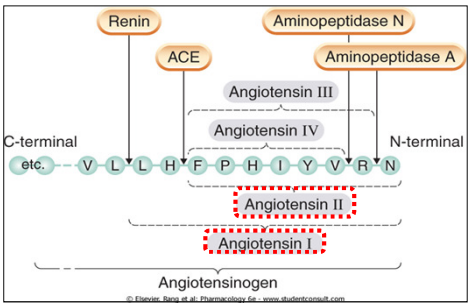
- Relaxation - ↓Ca^{2+} (↓BP)
  - Natriuretic peptide receptor → cGMP
  - Prostanoid receptor EP3 (IP) → cAMP
  - Inward rectifying K^+ channel (K_{IR}) → K^+

Peripheral vascular resistance

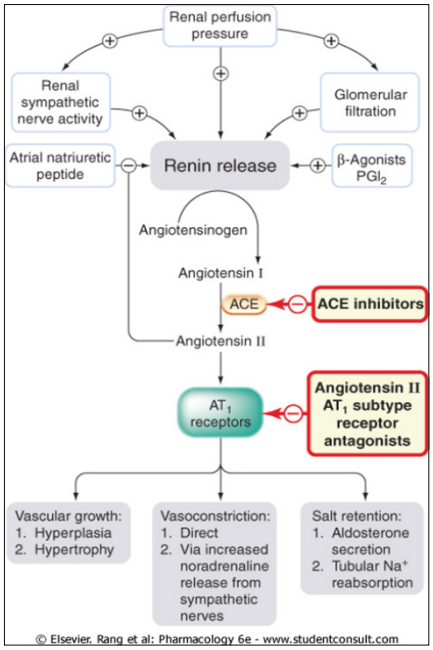
Regulation of vascular smooth muscle



- Activation of RAAS:
  - ↓renal blood flow (CHF/ renal stenosis)
  - ↓ [Na^+] in distal tubule
  - β-adrenoreceptor agonists
  - PGI_2
- Deactivation of RAAS
  - Natriuretic peptide
  - Angiotensin II (feedback)



RAAS



RAAS

- Angiotensin II
  - 40x as effective as adrenaline in raising BP by acting on:
    1. Vascular smooth muscle contraction (AT_1 receptor)
    2. ↑Aldosterone secretion

↓

↑ Na^+ reabsorption

↓

↑ Water retention

↓

↑BP

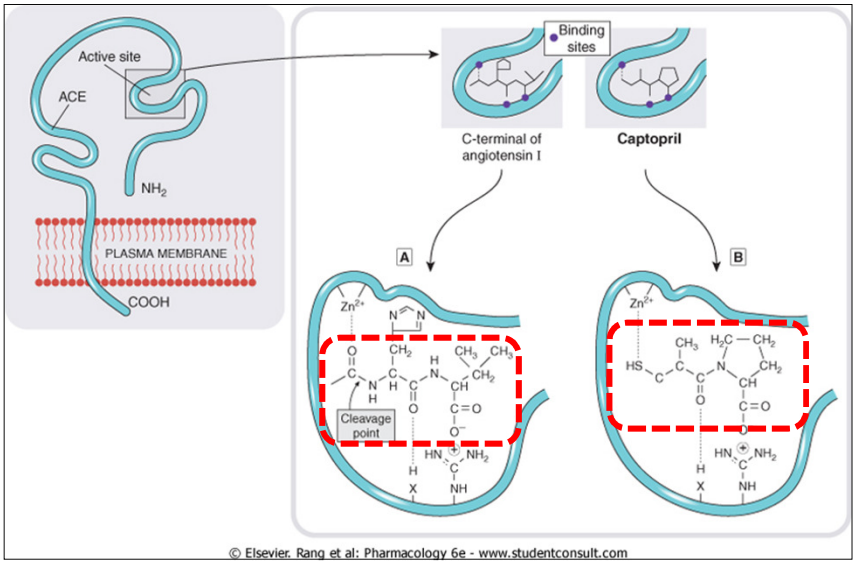
Targeting the RAAS

- Currently two available drug targets
  - Angiotensin converting enzyme (ACE)
  - Angiotensin II receptor (AT_1)

ACE inhibitors

- Indirectly acting vasodilators
- Blocks the RAAS by inhibiting the conversion of Angiotensin I to Angiotensin II
- 1st generation
  - captopril
  - enalapril
  - lisinopril
- 2nd generation
  - perindopril
  - ramipril
  - quinapril

ACE inhibitors



ACE inhibitors

Captopril / Captopril + Hydrochlorothiazide

- Indications
  - Mild - moderate hypertension
  - CHF
  - Left ventricular dysfunction after MI
- Dosage for hypertension
  - 25 - 50 mg 2-3x daily (Max 150 mg daily)
  - 25 mg daily Hydrochlorothiazide
  - Combination therapy = 1x daily - COMPLIANCE

ACE inhibitors

Enalapril / Enalapril + Hydrochlorothiazide

- Indications
  - Mild - moderate hypertension
  - CHF (in combination with diuretic and digoxin)
  - Asymptomatic left ventricular dysfunction
- Dosage for essential hypertension
  - 10 - 20 mg daily
  - 12.5 mg daily Hydrochlorothiazide
  - Combination therapy = 1x daily - COMPLIANCE

ACE inhibitors

Side effects

- **Dry cough (bradykinin accumulation)**
- Taste disturbances
- Hypotension
- **Hyperkalemia in combination with K^+-sparing diuretics**
- **Hyponatreamia**
- **Reversible renal failure**
  - Never prescribe ACE inhibitors to patients with renal stenosis
- Photosensitivity

ACE inhibitors

Contraindications

- Pt's with renal artery stenosis
- Pregnancy

Angiotensin II receptor blockers (ARBs)

- Indirectly acting vasodilators
- Blocks the RAAS by acting as a reversible competitive antagonist of angiotensin II
- Drugs:
  - valsartan
  - losartan
  - candesartan
  - irbesartan

ARBs

- Effects on heart:
  - ↓ contractility
  - ↓ venticular hypertrophy
  - ↓ sympathetic stimulation
- Effects on vasculature:
  - Vasodilation
  - ↓ growth and proliferation
- Other effects:
  - ↓ aldosterone and vasopressin secretion

ARBs

Valsartan / Valsartan + Hydrochlorothiazide

- Indications
  - Mild - moderate hypertension
  - CHF
  - Improves survival after MI
- Dosage for hypertension
  - 80 -160 mg once daily (Max 320 mg)
  - 12.5 mg daily Hydrochlorothiazide
  - Combination therapy = 1x daily - COMPLIANCE

ACE inhibitors

Losartan / Losartan + Hydrochlorothiazide

- Indications
  - Hypertension
- Dosage for essential hypertension
  - 50 mg daily (Max 100 mg)
  - 12.5 mg daily Hydrochlorothiazide
  - Combination therapy = 1x daily - COMPLIANCE

ARBs

Side effects

- Hypotension
- **Hyperkalemia in combination with K^+-sparing diuretics**
- Dizziness

ARBs

Contraindications

- Renal impairment
- Pregnancy

NSAIDs and Hypotensive drugs

- NSAID treatment can nullify the therapeutic effects of antihypertensive drugs by:
  - ↑ Na^+ and H_2O reabsorption in the nephron
  - ↓ Prostaglandin synthesis
- The dosage and duration of NASIAD therapy will determine the reversal of antihypertensive effects
- **NB! NSAIDs + ACEIs / ARBs + diuretics = renal failure**