Vasoactive Peptides

- Angiotensin
- Plasmakinin
- Vasopressin
- Natriuretic Peptides (NP)
- Vasoactive Intestinal Polypeptide (VIP)
- Substance P

Angiotensin

- Angiotensin is a peptide hormone that causes vasoconstriction.
- It is a part of the renin-angiotensin system.
- The renin-angiotensin system (RAS) or the renin-angiotensin-aldosterone system (RAAS) is a hormone system that regulates blood pressure and fluid balance.

The renin-angiotensin system (RAS)

- When blood pressure is reduced, the renal blood flow is reduced, juxtaglomerular cells in the kidneys feel ischemia and convert the pro-renin into renin and secrete it directly into the circulation.
- Plasma renin convert angiotensinogen (released by the liver) to angiotensin I.
- Angiotensin I (ANG I) is subsequently converted to angiotensin II (ANG II) by the enzyme angiotensin-converting enzyme (ACE) found in the lungs and kidney.
- Angiotensin II acts by binding angiotensin receptors and cause

  → Potent direct vasoconstrictor (VC).

  → Increase secretion of aldosterone Na+ and water retention.

  Increase sympathetic activity (increase NE release).

  Increases secretion of ADH and ACTH, stimulate drinking.

  A Stimulate glucocorticoid synthesis.

- Angiotensin II is degraded to angiotensin III and angiotensin IV.

Angiotensin II Receptors			
	Signal	**Main Location**	**Main Function**
AT_1	Gq	Heart, blood vessels,kidney, adrenal cortex, lung and brain.	- Potent VC, aldosterone, vasopressin,↑central sympathetic outflow.
AT_2	Gi	Present at high density in all tissues during fetal development, but less abundant in adult (adrenal medulla, reproductive tissue, vascular endothelium and parts of brain)	- Fetal tissue development, inhibition of proliferation, cell differentiation, Apoptosis vasodilatation.
AT_3 - AT_4	- Unclear mechanism.		

Actions	**Blood vessels**	- Angiotensin II (ANG II) is a very potent presser agent. - ANG II approximately 40 times more potent than NE. - ANG II is rapid in onset (10-15 seconds).
	Kidney & Adrenal glands	**- Adrenal Medulla:** - ANG II stimulate autonomic ganglia increase release of epinephrine and norepinephrine. **- Adrenal Cortex:** - ANG II stimulate aldosterone synthesis & release. - At high concentration ANG II stimulate glucocorticoid synthesis. **- Kidney:** - ANG II cause renal VC, inhibit renin release and increase Na+ reabsorption from proximal tubules.
	brain	- ANG II increase sympathetic outflow (increase NE). - ANG II stimulate drinking (increase thirst; dipsogen). - ANG II increases the secretion of ADH and ACTH.
	Cell growth	- ANG II is mitogenic for vascular and cardiac muscle cells and may development of cardiovascular hypertrophy, this effect is mediated by other pathways. - Over activity of renin-angiotensin system may development of hypertensive vascular disease.

inhibition Of The Renin-Angiotensin System

1) Drug That Block Renin Release.
2) Angiotensin-Converting Enzyme (ACE) Inhibitors.
3) Angiotensin II Receptor Blockers (ARBS).
4) Direct Renin Inhibitors.

1) Drug That Block Renin Release

- Clonidine is an α2 agonist (centrally and peripherally), It inhibits renin release by causing central reduction of renal sympathetic activity.
- Propranolol and other B-blockers inhibits renin release by blocking the intrarenal and extrarenal B-receptors which control neural renin release.

2) Angiotensin-Converting Enzyme (ACE) Inhibitors

Captopril (Capoten®)	**Lisinopril (Zestril®)**	**Enalapril (Renitec®)**
Fosinopril (Monopril®)	**Perindopril (Coversyl®)**	**Ramipril (Tritace®)**
Benazepril (Cibacen®)	**Cilazapril (Zapritens®)**	**Imidapril (Tanatril®)**
Zofenopril (Zofecard®)	**Quinapril (Accupril®)**	**Trandolapril (Mavik®)**

- ACE inhibitors are easily identifiable by their common suffix, 'pril'.
- All of the ACE inhibitors are orally bioavailable as a drug or prodrug.
- All of the ACE inhibitors are given as prodrug to improve oral bioavailability, except Captopril and Lisinopril , so these agents may be preferred in patients with severe hepatic impairment.
- Captopril is the first ACE inhibitor, and has a shorter duration of action.
- Enalapril is an oral prodrug that is converted to Enalaprilat.
- Enalaprilat is the only drug in this class available intravenously.
- Fosinopril is the only ACE inhibitor that is not eliminated primarily by the kidneys and does not require dose adjustment in patients with renal impairment.
- Perindopril, Ramipril, Cilazapril, imiapril, Quinapril, Trandolapril , Benazepril and Zofenopril are given as prodrug.

MECHANISM OF ACTION

The hypotensive activity of ACE inhibitors, due to;

- Blocks the conversion of angiotensin I to angiotensin II.
- Inhibits the degradation of bradykinin (vasodilator peptide, cause vasodilatation via NO release) (see next lecture).

Vasodilation of both arterioles and veins occurs as a result of,

- Decreased vasoconstriction (V angiotensin II).
- Enhanced vasodilation (↑ bradykinin).

Cardiac output and heart rate are not significantly changed.

THERAPEUTIC USES

Hypertension (used alone or in combination).

- First-line drugs for hypertensive patients with diabetes, chronic kidney disease, and patients at increased risk of coronary artery disease.

- **Heart failure and after myocardial infarction** (see CVS chapter).

Chronic kidney disease and diabetic nephropathy (kidney complications of diabetes mellitus), this effect result from;

- Improve intra renal hemodynamics with decrease glomerular efferent arteriolar resistance (VD) ⍰ decrease intraglomerular capillary pressure.
    - So, ACE inhibitors slow the progression of diabetic nephropathy and decrease albuminuria.
    - Now this drugs recommended in diabetes even in the absence of hypertension.
    - ACE inhibitors reduce the incidence of diabetes in patients with high cardiovascular risk.

SIDE EFFECTS

- Hypotension after initial dose.
- Dry persistence cough and angioedema (20% or more of patients); due to increase levels of bradykinin and substance P (inflammatory mediator), this effect resolves within a few days of discontinuation.
    - Bradykinin induce the production of arachidonic acid metabolites (increase prostaglandins) and nitric oxide (NO), which may promote cough through proinflammatory mechanisms.
    - ACE inhibitor cough can be treated by (two studies suggested);
        - Iron supplements (e.g. ferrous sulfate) an inhibitor of NO synthase.
        - Non-steroidal anti-inflammatory drugs; NSAIDS (e.g. aspirin 500 mg/day) an inhibitor of prostaglandins (PGs) synthesis.
- Hyperkalemia; due to decrease in aldosterone levels, Since aldosterone is responsible for increasing the excretion of potassium.
- Acute renal failure (renal impairment), particularly in patient with renal artery stenosis (narrowing of kidneys arteries).

DRUG INTERACTIONS

- K+ sparing diuretics or K+ supplements Increase hyperkalemia.
- NSAIDS; due to decrease prostaglandins (PGs) synthesis □ may reduce the hypotensive effects of ACE inhibitors.
- Lithium may increase blood concentrations of lithium

Contraindication

- Pregnancy (FDA category D):
    - ACE inhibitors are contraindicated during the second and third trimesters of pregnancy, because of the risk of fetal hypotension, anuria and renal failure, sometimes associated with fetal malformation (fetal lung hypoplasia and skeletal deformities) or fetal death.
- Patient who has experienced angioedema during therapy with any other ACE inhibitor.

3) Angiotensin II Receptor Blockers (ARBS)

Losartan (Cozaar®)	**Valsartan (Diovan®)**	**Candesartan (Atacand®)**
Irbesartan (Aprovel®)	**Eprosartan (Teveten®)**	**Telmisartan (Micardis®)**
Olmesartan (Erastapex®)	**Fimasartan (Kanarb®)**	**Azilsartan (Edarbi®)**

- Angiotensin receptor blockers (ARBS) are easily identifiable by their common suffix, 'sartan'.
- ARBS are competitive antagonists of the angiotensin II type 1 (AT1) receptor.
- Losartan and Valsartan were the first marketed.

- All of the ARBS are orally active and are dosed once-daily, except Valsartan which is twice a day.
- All of the ARBS are highly plasma protein binding.
- All of the ARBS are have large volumes of distribution, except Candesartan.
- Irbesartan, Eprosartan, Telmisartan and Olmesartan are also available.
- Fimasartan and Azilsartan are newer agents.

ACEIs Vs ARBs

- ARBS are have no effect on bradykinin metabolism.
- ARBS more selective blockers of angiotensin effect than ACE inhibitors.
- ARBS also have the potential for more complete inhibition of angiotensin action compared with ACE inhibitors, because there are enzymes other than ACE that are capable generation angiotensin II.
- ARBS have a similar benefits to those of ACE inhibitors in patients with hypertension, heart failure and chronic kidney disease.
- ARBS have a similar drug interaction to ACE inhibitors.
- ARBS have a similar adverse effects to ACE inhibitors, but less common.
- ARBS have a similar hazard to ACE inhibitors of use during pregnancy.

4) Direct Renin Inhibitors

Aliskiren (Tekturna®)

- Aliskiren is the first and only drug available in a class of drugs called direct renin inhibitors (FDA approval in 2007).
- It is act by binding to active site of renin decreasing plasma renin activity inhibiting conversion of angiotensinogen to angiotensin I.
- It is used in treatment of hypertension (alone or in combination with other antihypertensive agents).
- It has long duration of action, used once daily.
- ***Adverse effects:***

  Diarrhea and GI symptoms.
  Rash (hypersensitivity).
  Symptoms of hypotension e.g. headache and dizziness (after initiation treatment).
  Angioedema and cough; but less common, than ACE inhibitors or ARBS.
  May cause hyperkalemia.
- ***Contraindication:***

  Pregnancy; drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus (same as ACE inhibitors and ARBS).

- ***Drug interactions: with***

  ARBS or ACEI increase risk of renal impairment, hyperkalemia, and hypotension.
  K+ sparing diuretics or K+ supplements ↑ hyperkalemia.
  NSAIDS May reduce the hypotensive effects.
  LMEIS e.g. Erythromycin metabolism of Aliskiren increase it is effect.