PHARMACOLOGY

Drugs & the Renin-Angiotensin-Aldosterone System (RAAS)

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DISCLOSURE

None

Use Statement

OBJECTIVES

1. Identify disease states that utilize drugs with actions on the renin-angiotensin-aldosterone system (RAAS) in their management
2. Explain the mechanism of action of angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and direct renin inhibitors and correlate to underlying pathophysiology
3. Compare and contrast the effects of angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and direct renin inhibitors on renin, bradykinin, and glomerular filtration rate
4. State adverse effects and contraindications to angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and direct renin inhibitors
5. Describe the clinically important drug interactions of angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and direct renin inhibitors

A 38-year-old woman who is a veteran comes to the emergency department because of a 4-hour history of a sensation of tightness in her throat and swelling of her face, lips, and tongue. She has not had itching. During the past 3 weeks, she has had two similar, milder episodes that resolved without treatment within 24 to 72 hours. Six weeks ago, she began treatment with an ACE inhibitor for hypertension. She has seasonal allergies. Her temperature is 37.1°C (98.8°F), pulse is 80/min, respirations are 20/min, and blood pressure is 138/81 mm Hg. Physical examination shows angioedema of the lips and tongue. There is no evidence of urticaria. Which of the following is the most likely cause of the angioedema in this patient?

(A) Bradykinin

(B) Histamine

(C) Leukotriene B4

(D) Nitric oxide

(E) Prostaglandin E2

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INTRO TO THE RAAS

PHARM MODULATION OF EXTRACELLULAR FLUID

To increase or decrease body fluid volume, the kidneys must increase or decrease renal Na+ reabsorption from the volume of glomerular filtrate

- Accomplished by integrated action of apical and basolateral ion channels and transporters

Pharmacologic modulators of extracellular fluid volume include agents that

1. Modify neurohormonal volume regulators (e.g., ACEIs and ARBs)
2. Act directly on the nephron segments to alter renal Na+ handling

PHARM MODULATION OF EXTRACELLULAR FLUID

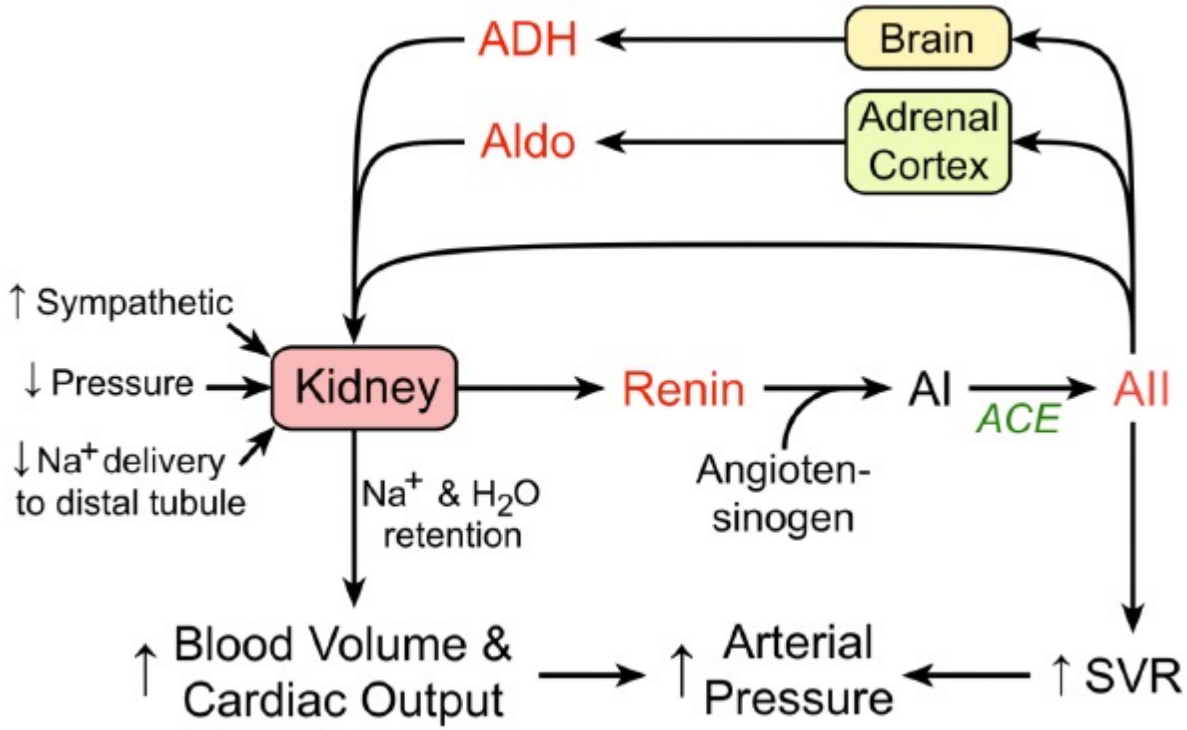
Drugs that modify neurohormonal volume regulators work on RAAS

- Angiotensin converting enzyme inhibitors (ACEIs)
- Angiotensin II receptor blockers (ARBs)
- Direct renin inhibitors
- Aldosterone antagonists

ACTIVE LEARNING

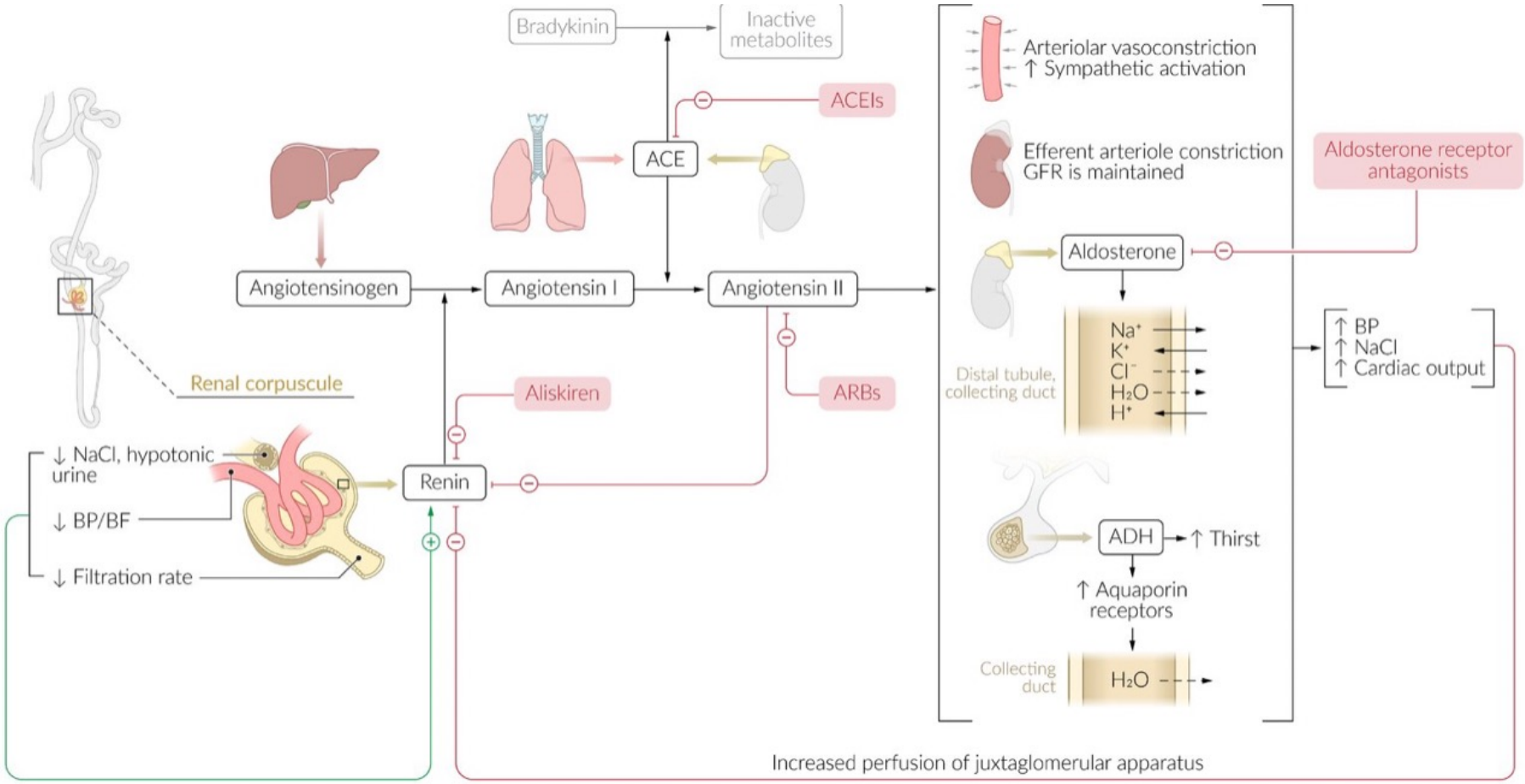
In one minute, write down what you remember about the RAAS.

RAAS



ADH = antidiuretic hormone
Aldo = aldosterone
AI = angiotensin I
AII = angiotensin II
SVR = systemic vascular resistance

RAAS & SITES OF DRUG ACTIONS

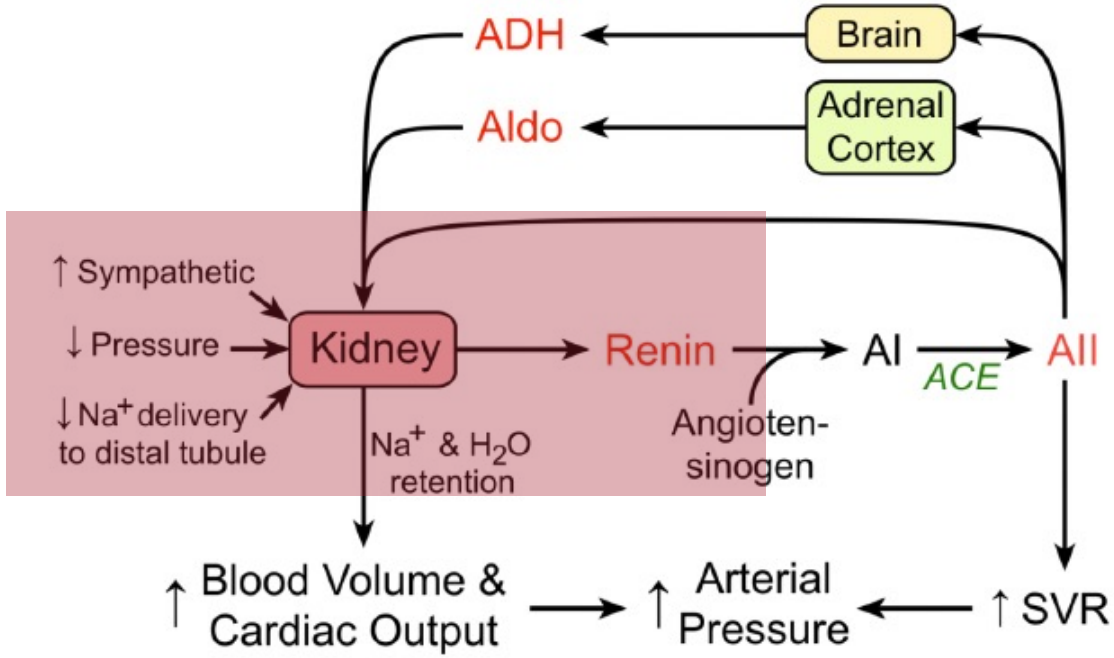


RENIN

Proteolytic enzyme released into the circulation by the kidneys

Release stimulated by

- Sympathetic nervous system activity (via B-1 receptors)
- Renal artery hypotension (systemic hypotension or renal artery stenosis)
- Decreased sodium delivery to the distal tubules

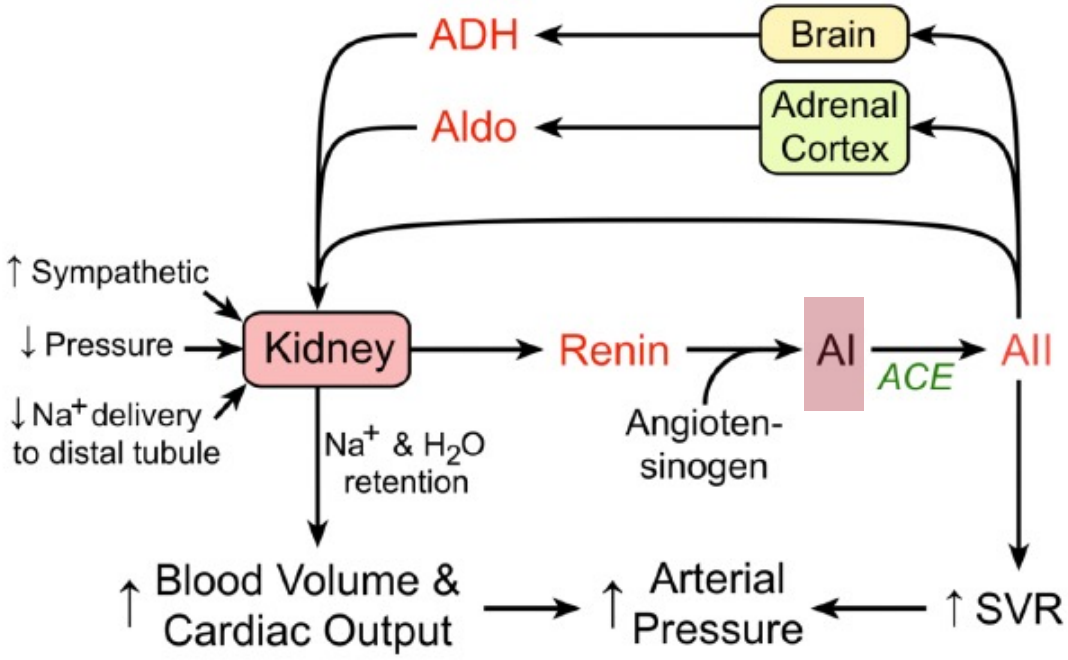


ANGIOTENSIN I (AI)

Physiologically INACTIVE

Requires conversion

- Renin converts angiotensinogen to angiotensin I

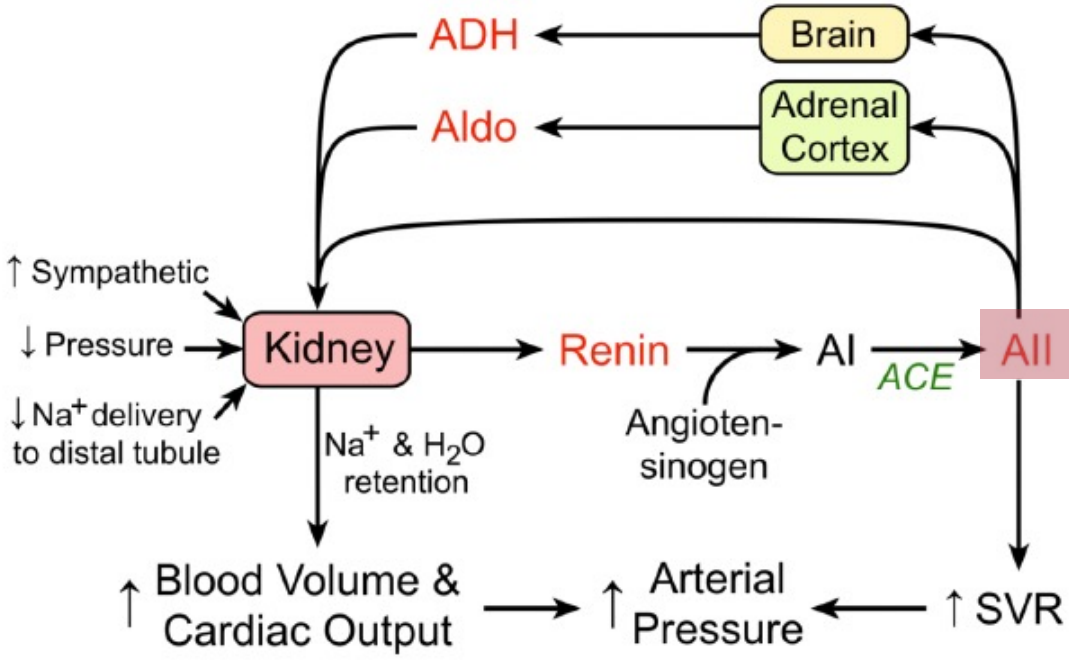


ANGIOTENSIN II (AII)

Physiologically ACTIVE

Requires conversion

- Angiotensin-converting enzyme converts angiotensin I to angiotensin II



ANGIOTENSIN II

Blood vessel

Tense

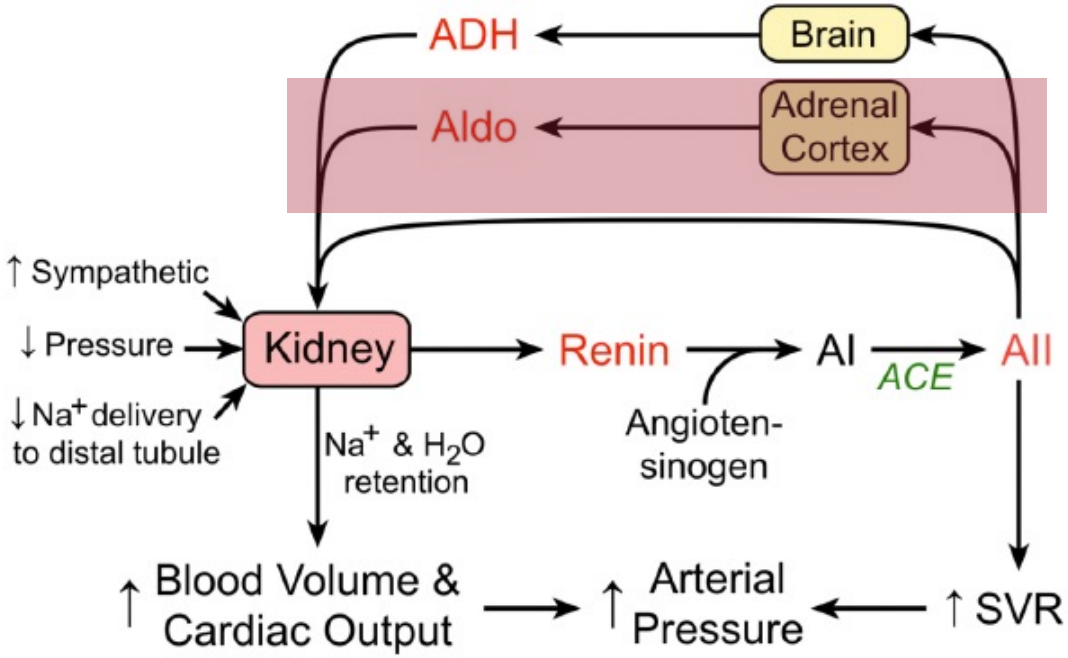
1. Angiotensin II causes **vasoconstriction** throughout the body
   - Receptors in vascular smooth muscle
2. Binds angiotensin II receptors primarily in efferent arterioles
3. Acts on the cells that line the proximal convoluted tubule, making them reabsorb more sodium ions from the filtrate
4. Acts on hypothalamus and stimulates thirst and increases antidiuretic hormone (increases water reabsorption)
5. Stimulates adrenal glands (zona glomerulosa) to secrete aldosterone
   - Aldosterone promotes water and sodium retention

ALDOSTERONE

Sodium retention in the ECF compartment largely regulated by aldosterone

Causes Na+ reabsorption in exchange for K+ via the epithelial sodium channel (eNaC channel) in collecting duct

- SPIRONOLACTONE and EPLERENONE are antagonists of the mineralocorticoid receptor
- AMILORIDE and TRIMETHOPRIM (an antibiotic) block the eNaC channel itself



ACTIVE LEARNING

Consider the following components of the RAAS:

A. Aldosterone
B. Angiotensin I
C. Angiotensin II
D. Renin

Which is physiologically inactive?

Which converts angiotensinogen to angiotensin I?

Which is physiologically active and requires conversion by angiotensin-converting enzyme?

Which largely regulates sodium retention in the ECF compartment?

PHARM STRATEGIES TO INHIBIT THE RAAS

1. Beta-adrenergic receptor antagonists

- Inhibit renin release by juxtaglomerular cells in kidney

2. Direct renin inhibitors

- Inhibit renin's action on angiotensinogen → ↓ formation of angiotensin I and angiotensin II → ↓ secretion of aldosterone
  - Inhibits water and Na+ retention

PHARM STRATEGIES TO INHIBIT THE RAAS

3. Angiotensin converting enzyme inhibitors

- Prevent conversion of ATI to ATII which prevents secretion of aldosterone
  - Inhibits water and Na+ retention

4. Angiotensin II receptor blockers

- Compete with ATI receptors in the adrenal cortex inhibiting release of aldosterone
  - Inhibits water and Na+ retention

5. Aldosterone antagonists

- Competitively antagonize aldosterone binding to its receptor
  - Inhibits water and Na+ retention

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ANGIOTENSIN CONVERTING ENZYME INHIBITORS (ACEIs)

ANGIOTENSIN II

Blood vessel

Tense

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   - Receptors in vascular smooth muscle
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ANGIOTENSIN-CONVERTING ENZYME (ACE)

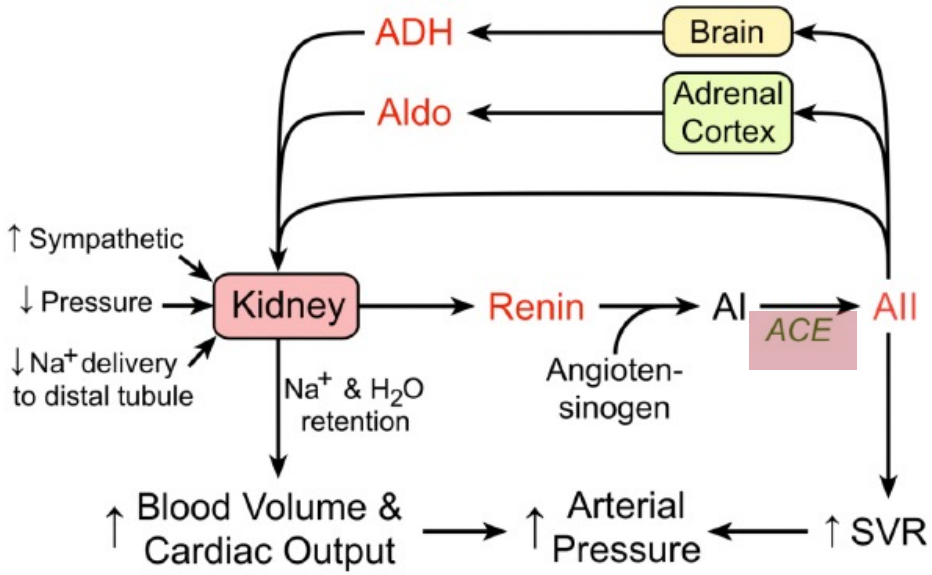
ACE found in endothelial cells in general, but mostly those lining the vessels in the lungs

Converts angiotensin I to angiotensin II

- ACE cleaves two amino acids from angiotensin I leaving angiotensin II

ACE breaks down bradykinin

- Bradykinin is a vasodilator and involved in inflammation
- Bradykinin causes bronchoconstriction and cough



ACTIVE LEARNING

Now that you understand the role of angiotensin II and angiotensin-converting enzyme (ACE), how would you expect an ACE inhibitor to impact:

- Angiotensin II levels
- Vasculature
- Aldosterone
- Water and sodium retention
- Renin
- Bradykinin

ACE INHIBITOR MECHANISM OF ACTION

Inhibit angiotensin-converting enzyme

- Prevents conversion of angiotensin I to angiotensin II
- Less angiotensin II → ↓ vasoconstriction, ↓ Na+ reabsorption in the proximal convoluted tubule, ↓ ADH secretion, ↓ aldosterone secretion
- Prevents inactivation of bradykininn

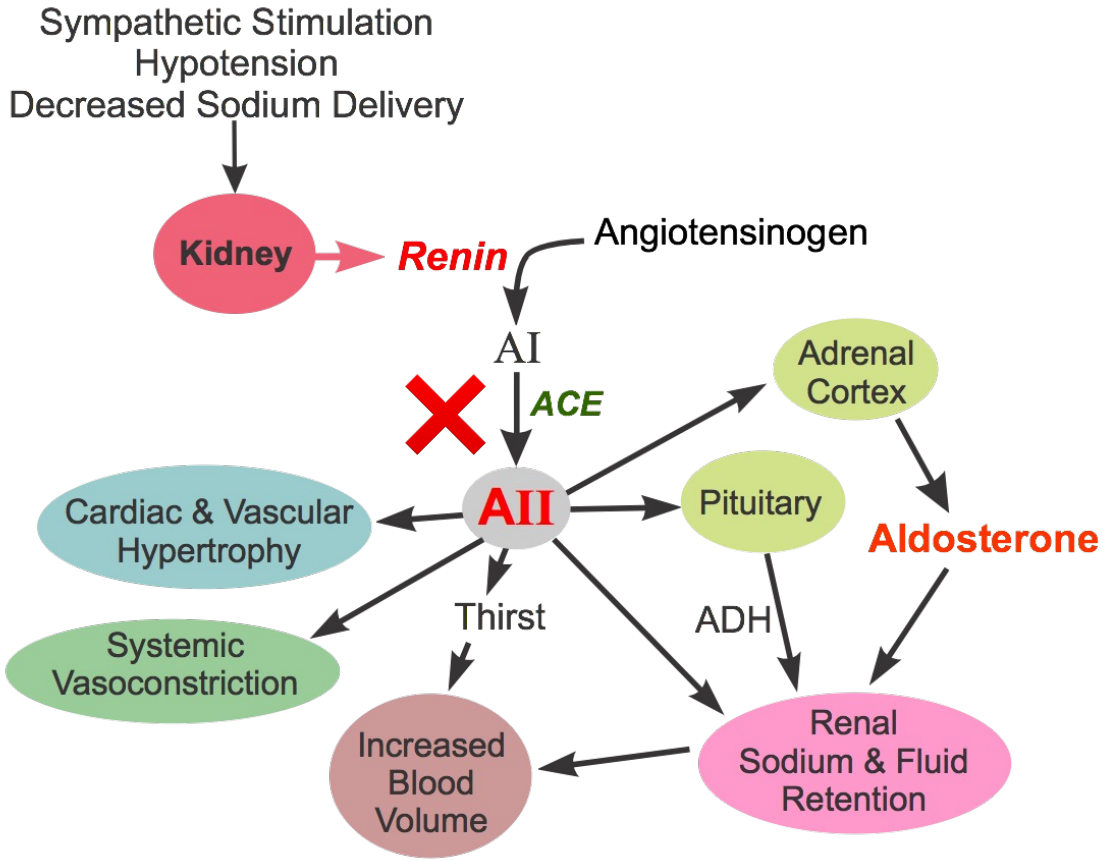
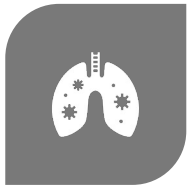


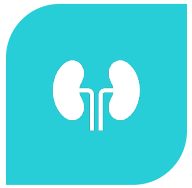
Image credit:
https://cvpharmacology.com/vasodilator/renin

SALIENT ADVERSE EFFECTS OF ACE INHIBITORS



COUGH

INCREASED BRADYKININ LEVELS



RENAL INSUFFICIENCY

DECREASED GLOMERULAR FILTRATION

HYPOTENSION

DECREASED VASOCON-STRICTION

ANGIOEDEMA

INCREASED BRADYKININ LEVELS

HYPERKALEMIA

DECREASED ALDOSTERONE

TERATOGEN

AVOID USE IN PREGNANCY

ACEIs

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Captopril Enalapril Lisinopril Ramipril Enalaprilat 💉 Others ***-pril***	**Pregnancy** Bilateral renal artery stenosis Angioedema	**C**ough **A**ngioedema **P**regnancy problems (teratogen) **T**aste change **O**rthostatic hypotension **P**otassium increase **R**enal artery stenosis (contraindication) **I**ncreased renin **L**eukopenia ***"CAPTOPRIL"***	Potassium supplements and potassium-sparing diuretics (spironolactone) may cause hyperkalemia when combined with ACEIs NSAIDS and aspirin may reduce the antihypertensive response to ACEIs (bradykinin stimulates prostaglandin synthesis which contributes to the hypotensive effects of ACEIs) DPP4 inhibitors, alteplase, everolimus, pregabalin ↑ risk of angioedema

CLINICAL USE & ADME

Cardiovascular disease (hypertension, left ventricular systolic dysfunction, acute myocardial infarction, diabetes with high risk of cardiovascular events)

Heart failure

Diabetic nephropathy

Most oral

- Enalaprilat injectable

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ANGIOTENSIN II RECEPTOR BLOCKERS (ARBs)

ARB MECHANISM OF ACTION

ARBs competitively bind to the AT-1 receptor

- Theoretically surmountable, but functionally insurmountable
- Sustained receptor blockade

Inhibit most of the effects of angiotensin II

- ↓ vasoconstriction, ↓ Na+ reabsorption in the proximal convoluted tubule, ↓ ADH secretion, ↓ aldosterone secretion

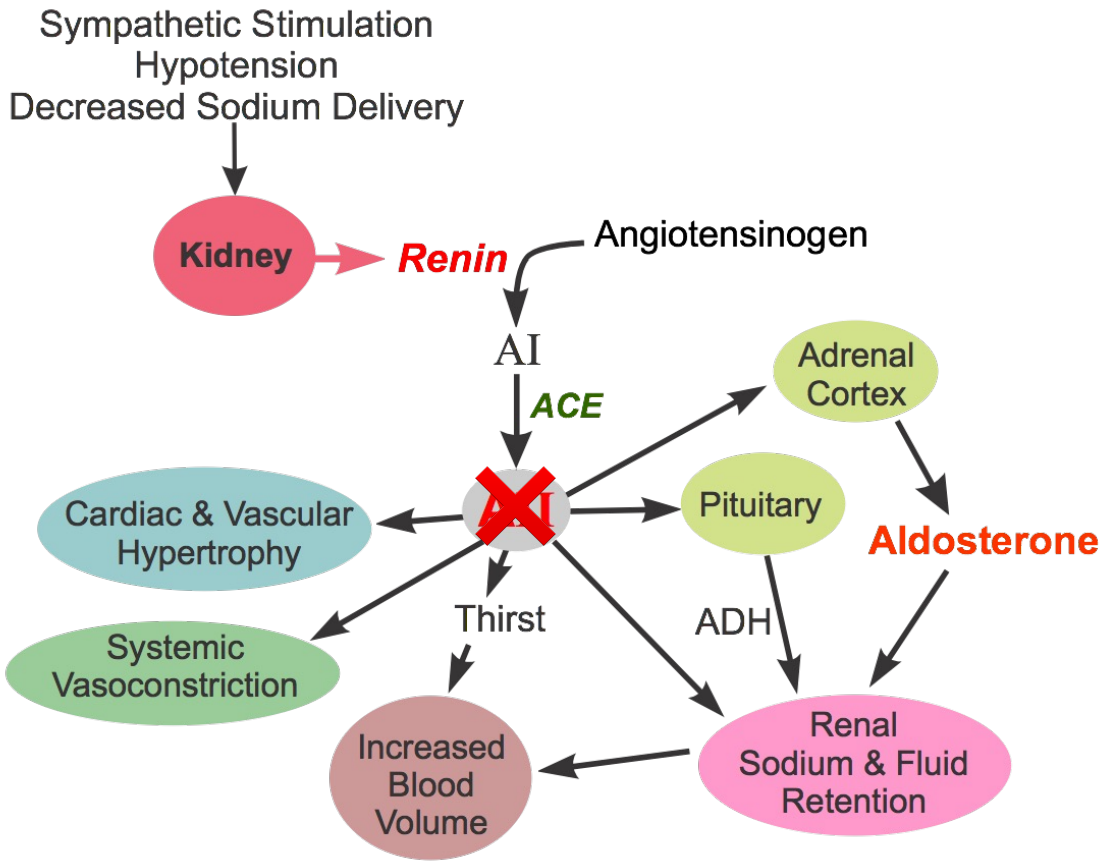
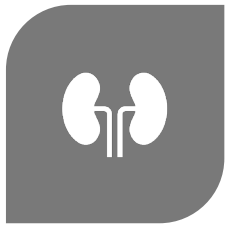


Image credit:
https://cvpharmacology.com/vasodilator/renin

ACTIVE LEARNING

Based on the mechanism of action, do ARBs directly impact bradykinin levels? Compared to ACE inhibitors, would you expect ARBs to be associated with more, less, or the same incidence of cough and angioedema?

SALIENT ADVERSE EFFECTS OF ARBs



RENAL INSUFFICIENCY

DECREASED GLOMERULAR FILTRATION

HYPOTENSION

DECREASED VASOCONSTRICTION

ANGIOEDEMA

LESS THAN ACE INHIBITORS

HYPERKALEMIA

DECREASED ALDOSTERONE

TERATOGEN

AVOID USE IN PREGNANCY; CONGENITAL MALFORMATIONS

ARBs

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Candesartan cilexetil Irbesartan Losartan Olmesartan medoxomil Valsartan ***-sartan***	Pregnancy Patients < 1 year old	Hyperkalemia Decreased GFR, renal failure Angioedema Hypotension Leukopenia Hepatitis	Potassium supplements and potassium-sparing diuretics (spironolactone) may cause hyperkalemia when combined with ARBs

CLINICAL USE & ADME

Same as ACE inhibitors

Cardiovascular disease (hypertension, left ventricular systolic dysfunction, acute myocardial infarction, diabetes with high risk of cardiovascular events)

Heart failure

Diabetic nephropathy

ADME varies based on individual ARB

Candesartan cilexetil, olmesartan medoxomil are prodrugs

ACE INHIBITORS & ARBs IN PREGNANCY

Known teratogens

Avoid in pregnancy

May result in

- Reduced fetal renal function
- Increased fetal and neonatal morbidity and death
- Oligohydramnios (fetal lung hypoplasia, skeletal deformations)

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DIRECT RENIN INHIBITORS

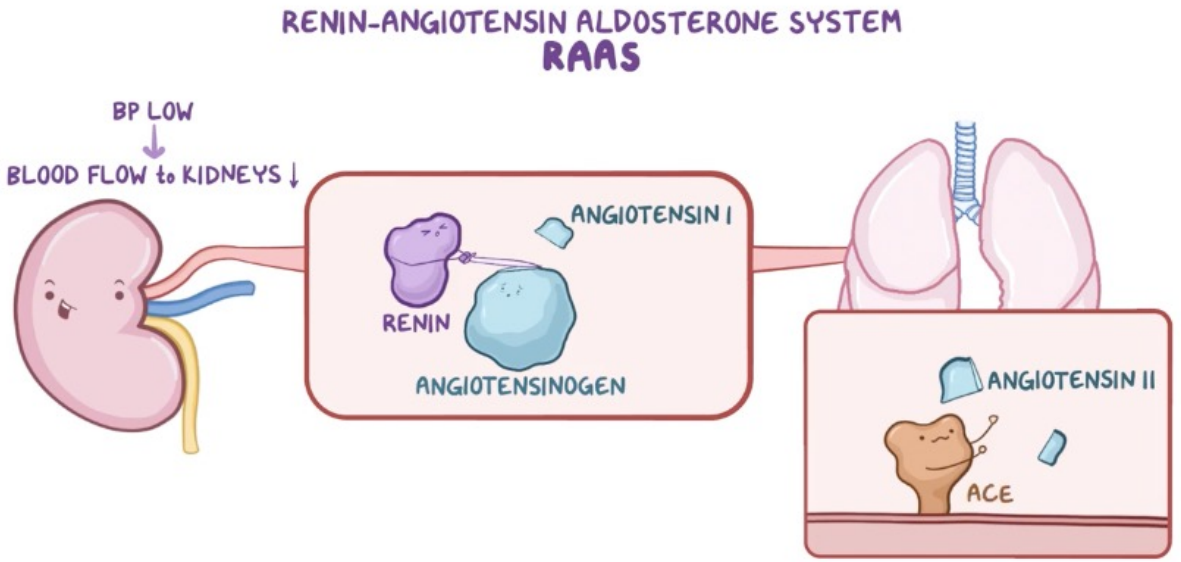
RAAS

RENIN

Renin converts angiotensinogen to angiotensin I

Angiotensin I is physiologically inactive

Angiotensin I is precursor to angiotensin II (highly physiologically active)

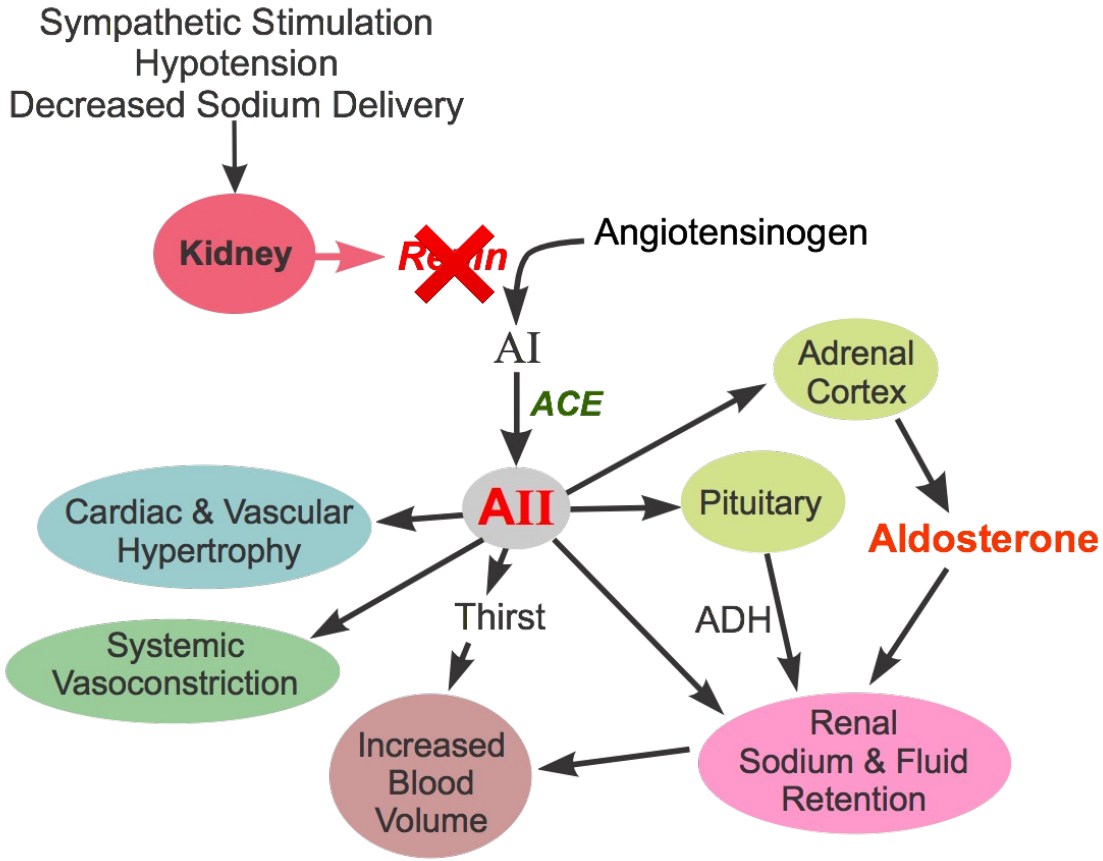


DIRECT RENIN INHIBITOR MECHANISM OF ACTION

Potent competitive inhibitor of renin

Prevents conversion of angiotensinogen to angiotensin I

- Thereby reducing angiotensin II
- ↓ vasoconstriction, ↓ Na+ reabsorption in the proximal convoluted tubule, ↓ ADH secretion, ↓ aldosterone secretion



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https://cvpharmacology.com/vasodilator/renin

DIRECT RENIN INHIBITOR

Name	CIs & Cautions	Adverse Effects	Selected Interactions
Aliskiren (Tekturna, Rasilez)	Pregnancy Using ACEI or ARB	Hyperkalemia Decreased GFR, renal failure Angioedema Hypotension	Reduces absorption of furosemide by 50% Aliskiren levels increased by ketoconazole, atorvastatin, cyclosporine (drugs that inhibit p-glycoprotein)

CLINICAL USE & ADME

Hypertension

Low bioavailability

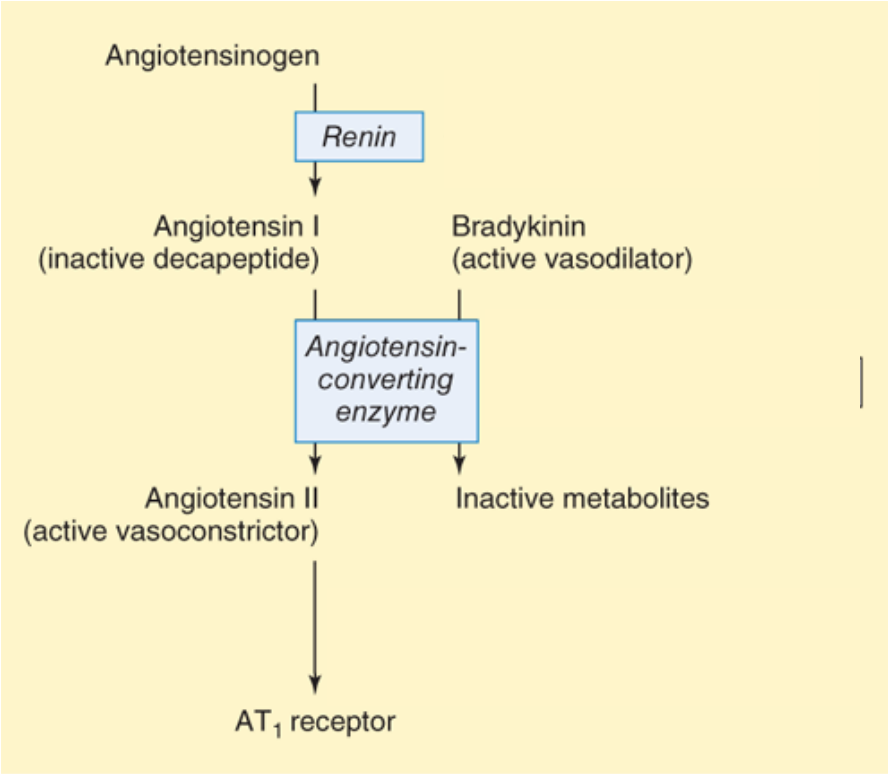
Substrate for P-glycoprotein

Low hepatic metabolism

ACTIVE LEARNING

Using the provided diagram, indicate where each of the following drug classes works in the RAAS.

- ACE inhibitors
- ARBs
- Direct renin inhibitors



ACTIVE LEARNING

Complete the following table with how you would expect the listed drugs of the RAAS to impact each parameter (↑, ↓, or =)

	Renin	Angiotensin I	Angiotensin II	Aldosterone	Bradykinin
ACE inhibitors					
ARBs					
Direct Renin Inhibitors					

IMPACT OF DRUGS ON RAAS

	ACE inhibitors	ARBs	Direct Renin Inhibitors
Renin	↑	↑	↑
Angiotensin I	↑	↑	↓
Angiotensin II	↓	↑	↓
Aldosterone	↓	↓	↓
Bradykinin	↑	=	=

IMPACT OF DRUGS ON RAAS

	Renin	Angiotensin I	Angiotensin II	Aldosterone	Bradykinin
ACE inhibitors	↑	↑	↓	↓	↑
ARBs	↑	↑	↑	↓	=
Direct Renin Inhibitors	↑	↓	↓	↓	=

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ANY QUESTIONS?