

## RENIN

*Not to be confused with **rennin**, the active enzyme in **rennet** (required for making cheese).*

**Renin** (pronounced "Ree-nin" or "Rē-nin" also known as **angiotensinogenase** is a circulating enzyme that participates in the renin-angiotensin system that mediates extracellular volume, arterial vasoconstriction, and consequently mean arterial blood pressure. The enzyme is secreted by the kidneys from specialized juxtaglomerular cells in response to decreases in glomerular filtration rate (a consequence of low blood volume), diminished filtered sodium chloride and sympathetic nervous system innervation. The enzyme circulates in the blood stream and hydrolyzes angiotensinogen secreted from the liver into the peptide angiotensin I. Angiotensin I is further cleaved in the lungs by endothelial bound angiotensin converting enzyme (ACE) into angiotensin II, the final active peptide. The normal concentration in adult human plasma is 1.98-24.6 ng/L in the upright position.

### Structure

An enzyme of the hydrolase class that catalyses cleavage of the leucine bond in angiotensin to generate angiotensin. The enzyme is synthesised as inactive prorenin in the kidney and released into the blood in the active form in response to various metabolic stimuli. Not to be confused with rennin (chymosin).

The primary structure of renin precursor consists of 406 amino acids with a pre and a pro segment carrying 20 and 46 amino acids respectively. Mature renin contains 340 amino acids and has a mass of 37 kD.

## Function

Renin activates the renin-angiotensin system by cleaving angiotensinogen, produced by the liver, to yield angiotensin I, which is further converted into angiotensin II by ACE, the angiotensin-converting enzyme primarily within the capillaries of the lungs. Angiotensin II then constricts blood vessels, increases the secretion of ADH and aldosterone, and stimulates the hypothalamus to activate the thirst reflex, each leading to an increase in blood pressure.

Renin is secreted from juxtaglomerular cells (of the afferent arterioles), which are activated via signaling (the release of prostaglandins) from the macula densa, which respond to the rate of fluid flow through the distal tubule, by decreases in renal perfusion pressure (through stretch receptors in the vascular wall), and by nervous stimulation, mainly through beta-1 receptor activation. A drop in the rate of flow past the macula densa implies a drop in renal filtration pressure. Renin's primary function is therefore to eventually cause an increase in blood pressure, leading to restoration of perfusion pressure in the kidneys.

Renin can bind to ATP6AP2, which results in a fourfold increase in the conversion of angiotensinogen to angiotensin I over that shown by soluble renin. In addition, renin binding results in phosphorylation of serine and tyrosine residues of ATP6AP2.

## Gene

The gene for renin, *REN*, spans 12 kb of DNA and contains 8 introns. It produces several mRNA that encode different *REN* isoforms.

## Secretion

Human Renin is secreted by at least 2 cellular pathways: a constitutive pathway for the secretion of prorenin and a regulated pathway for the secretion of mature renin.

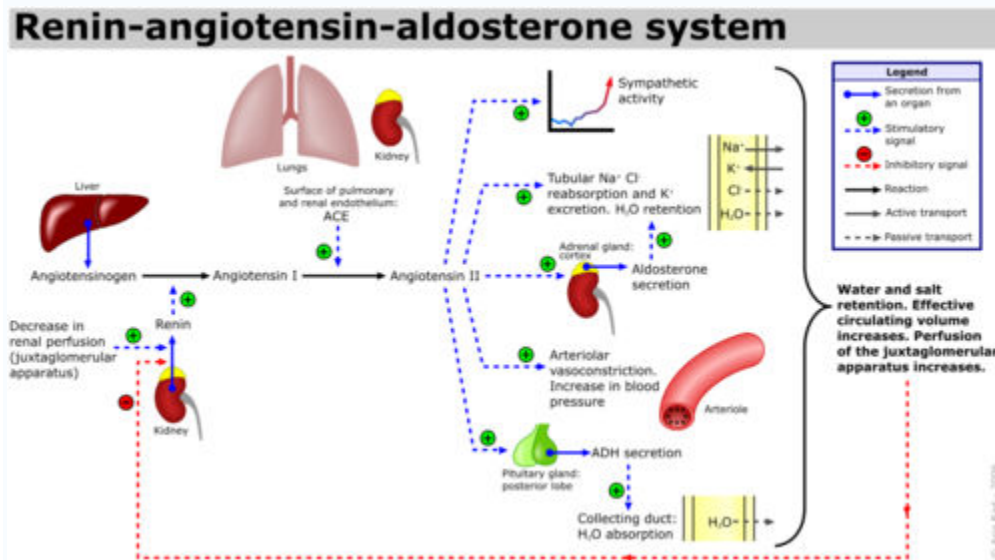
## Clinical implications

An over-active renin-angiotension system leads to vasoconstriction and retention of sodium and water. These effects lead to hypertension. Therefore, renin inhibitors can be used for the treatment of hypertension.

## Renin-angiotensin system

The **renin-angiotensin system** (RAS) or the **renin-angiotensin-aldosterone system** (RAAS) is a hormone system that helps regulate long-term blood pressure and extracellular volume in the body.

### Activation



Schematic depicting how the RAAS works. Here, activation of the RAAS is initiated by a low perfusion pressure in the juxtaglomerular apparatus

The system can be activated when there is a loss of blood volume or a drop in blood pressure (such as in a hemorrhage).

1. If the perfusion of the juxtaglomerular apparatus in the kidneys decreases, then the juxtaglomerular cells release the enzyme renin.
2. Renin cleaves an inactive peptide called *angiotensinogen*, converting it into *angiotensin I*.
3. Angiotensin I is then converted to *angiotensin II* by angiotensin-converting enzyme (ACE), which is found mainly in lung capillaries.
4. Angiotensin II is the major bioactive product of the renin-angiotensin system. Angiotensin II acts as an endocrine, autocrine/ paracrine, and intracrine hormone.

## Effects

Angiotensin I may have some minor activity, but angiotensin II is more potent. Angiotensin II has a variety of effects on the body:

- Throughout the body, it is a potent vasoconstrictor.
- In the kidneys, it constricts glomerular arterioles, having a greater effect on efferent arterioles than afferent. As with most other capillary beds in the body, the constriction of afferent arterioles increases the arteriolar resistance, raising systemic arterial blood pressure and decreasing the blood flow. However, the kidneys must continue to filter enough blood despite this drop in blood flow, necessitating mechanisms to keep glomerular blood pressure up. To do this, Angiotensin II constricts efferent arterioles, which forces blood to build up in the glomerulus, increasing glomerular pressure. The glomerular filtration rate (GFR) is thus maintained, and blood filtration can continue despite lowered overall kidney blood flow.
- In the adrenal cortex, it acts to cause the release of *aldosterone*. Aldosterone acts on the tubules (i.e. the distal convoluted tubules and the cortical collecting ducts) in the kidneys, causing

them to reabsorb more sodium and water from the urine. Potassium is secreted into the tubule in exchange for the sodium, which is reabsorbed. Aldosterone also acts on the central nervous system to increase a person's appetite for salt, and to make them feel thirsty.

- Release of Anti Diuretic Hormone (ADH) -- also called vasopressin -- ADH is made in the hypothalamus. ADH is stored and released from the pituitary gland.

These effects directly act to increase the amount of fluid in the blood, making up for a loss in volume, and to increase blood pressure.

### **Clinical significance**

The renin-angiotensin system is often manipulated clinically to treat high blood pressure.

- Inhibitors of angiotensin-converting enzyme (ACE inhibitors) are often used to reduce the formation of the more potent angiotensin II. Captopril is an example of an ACE inhibitor.
- Alternatively, angiotensin receptor blockers (ARBs) can be used to prevent angiotensin II from acting on angiotensin receptors.
- A new drug called Aliskiren is being released in 2007 which directly inhibits renin.

### **Other uses of ACE**

Interestingly, ACE cleaves a number of other peptides, and in this capacity is an important regulator of the kinin-kallikrein system.

### **Fetal renin-angiotensin system**

In the fetus, the renin-angiotensin system is predominantly a sodium-losing system, as angiotensin II has little or no effect on aldosterone levels. Renin levels are high in the fetus, while angiotensin II levels are significantly lower — this is due to the limited pulmonary blood

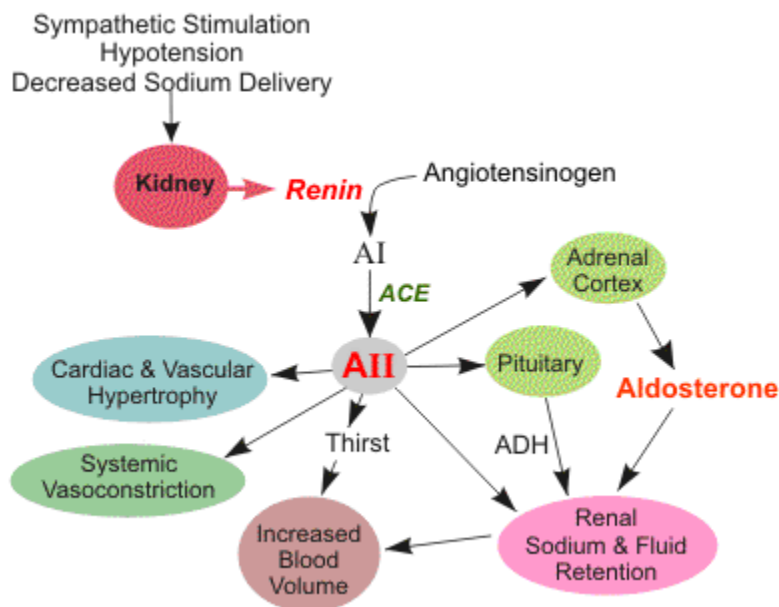
flow, preventing ACE (found predominantly in the pulmonary circulation) from having its maximum effect.

## Renin-Angiotensin-Aldosterone System

The renin-angiotensin-aldosterone system (RAAS) plays an important role in regulating blood volume and systemic vascular resistance, which together influence cardiac output and arterial pressure. As the name implies, there are three important components to this system: 1) renin, 2) angiotensin, and 3) aldosterone. Renin, which is primarily released by the kidneys, stimulates the formation of angiotensin in blood and tissues, which in turn stimulates the release of aldosterone from the adrenal cortex.

Renin is a proteolytic enzyme that is released into the circulation primarily by the kidneys. Its release is stimulated by

- 1) Sympathetic nerve activation (acting via  $\alpha$ -adrenoceptors)
- 2) Renal artery hypotension (caused by systemic hypotension or renal artery stenosis)
- 3) Decreased sodium delivery to the distal tubules of the kidney.



**Juxtaglomerular (JG) cells** associated with the afferent arteriole entering the renal glomerulus are the primary site of renin storage and release in the body. A reduction in afferent arteriole pressure causes the release of renin from the JG cells, whereas increased pressure inhibits renin release. Beta<sub>1</sub>-adrenoceptors located on the JG cells respond to sympathetic nerve stimulation by releasing renin. Specialized cells (**macula densa**) of distal tubules lie adjacent to the JG cells of the afferent arteriole. The macula densa senses the amount of sodium and chloride ion in the tubular fluid. When NaCl is elevated in the tubular fluid, renin release is inhibited. In contrast, a reduction in tubular NaCl stimulates renin release by the JG cells. There is evidence that prostaglandins (PGE<sub>2</sub> and PGI<sub>2</sub>) stimulate renin release in response to reduced NaCl transport across the macula densa. When afferent arteriole pressure is reduced, glomerular filtration decreases, and this reduces NaCl in the distal tubule. This serves as an important mechanism contributing to the release of renin when there is afferent arteriole hypotension.

When renin is released into the blood, it acts upon a circulating substrate, **angiotensinogen**, that undergoes proteolytic cleavage to form the decapeptide **angiotensin I**. Vascular endothelium, particularly in the lungs, has an enzyme, **angiotensin converting enzyme (ACE)**, that cleaves off two amino acids to form the octapeptide, **angiotensin II (AII)**, although many other tissues in the body (heart, brain, vascular) also can form AII.

AII has several very important functions:

- Constricts resistance vessels (via AII [AT<sub>1</sub>] receptors) thereby increasing systemic vascular resistance and arterial pressure
- Acts on the adrenal cortex to release **aldosterone**, which in turn acts on the kidneys to increase sodium and fluid retention

- Stimulates the release of vasopressin (antidiuretic hormone, ADH) from the posterior pituitary, which increases fluid retention by the kidneys
- Stimulates thirst centers within the brain
- Facilitates norepinephrine release from sympathetic nerve endings and inhibits norepinephrine re-uptake by nerve endings, thereby enhancing sympathetic adrenergic function
- Stimulates cardiac hypertrophy and vascular hypertrophy

The renin-angiotensin-aldosterone pathway is regulated not only by the mechanisms that stimulate renin release, but it is also modulated by natriuretic peptides (ANP and BNP) released by the heart. These natriuretic peptides act as an important counter-regulatory system.

Therapeutic manipulation of this pathway is very important in treating hypertension and heart failure. ACE inhibitors, AII receptor blockers and aldosterone receptor blockers, for example, are used to decrease arterial pressure, ventricular afterload, blood volume and hence ventricular preload, as well as inhibit and reverse cardiac and vascular hypertrophy.

## **Blood Pressure and Urine Protein Levels with the Least Risk for Worsening Kidney Disease**

Chronic kidney disease can cause a gradual and progressive loss of function in both kidneys. Most patients with chronic kidney disease have high blood pressure (hypertension) and high levels of protein in their urine (proteinuria). Doctors use drugs called antihypertensive agents to reduce both blood pressure and protein in urine. Some of these drugs, such as angiotensin-converting enzyme (ACE) inhibitors, clearly prevent worsening kidney function.

Guidelines recommend that blood pressure should be reduced to less than 130/80 mm Hg in patients with kidney disease. Some recommend reducing blood pressure to even lower levels (<125/75



mm Hg) in patients who lose more than 1 gram of protein in their urine per day. A few studies, however, suggest that reducing blood pressure too much may be harmful and increase the risk for heart attacks. Whether very low blood pressure could worsen kidney function is also questioned.

Worsening kidney disease is defined as either kidney failure or a doubling of serum creatinine levels, which are measured by a blood test that shows kidney damage. Higher systolic (the top number), but not diastolic (the bottom number), blood pressure was strongly related to risk for worsening kidney function. Risks for higher systolic pressure were marked in patients with urine protein levels greater than 1.0 gram daily and were not apparent in patients with urine protein levels less than 1.0 gram daily. Patients with systolic pressures of 110 to 129 mm Hg and urine protein levels of less than 1.0 gram daily had the lowest risk for worsening kidney disease. Very low systolic pressure (<110 mm Hg) was associated with increased risk for worsening kidney disease.

## **Renin Assay**

### **Hypertension/High Blood Pressure**

A renin assay blood test is done to find the cause of high blood pressure (hypertension). Renin is an enzyme made by special cells in the kidneys. Renin works with aldosterone (a hormone made by the adrenal glands) and several other substances to help balance sodium and potassium levels in the blood and fluid levels in the body, which affects your blood pressure.

A renin test is often done at the same time as an aldosterone test. In some people, it may be normal to have high blood levels of both renin and aldosterone. If renin levels are low and aldosterone levels are high, a tumor may be present in the adrenal glands. A renin test is done to find the cause of high blood pressure (hypertension), especially when potassium levels in the blood are low.

## How To Prepare

For 2 to 4 weeks before the test, you will be asked to stop taking medicines that can affect the test, such as diuretics, estrogens, and high blood pressure medicines (especially beta-blockers and ACE inhibitors). Your health professional may have you take other medicines for a few weeks that will not change the renin test results. Do not eat or drink foods that contain caffeine the day before the test. Natural licorice and caffeine can change the test results. For 3 days before a renin test, follow a special low-sodium diet. Do not eat or drink anything for 8 hours before the test.

## How It Is Done

You may need to sit or lie down to relax for 1 to 2 hours before your blood is collected. A second blood sample may be collected after you move around for 2 hours.

## Results

A renin assay blood test is done to find the cause of high blood pressure (hypertension). The time of day and your position (standing, sitting, or lying down) before the blood sample is collected, your age, and the level of sodium in your blood all affect the test results.

## Normal

Normal values may vary from lab to lab.

<b>Plasma renin activity</b>	
<b>Adult, ages 20–39 (upright position, normal-sodium diet):</b>	0.1–4.3 nanograms per milliliter per hour (ng/mL/hr)
<b>Adult, age over 40 (upright position, normal-sodium diet)</b>	0.1–3.0 ng/mL/hr
<b>Adult, ages 20–39 (upright position, low-sodium diet)</b>	2.9–24.0 ng/mL/hr

<b>Adult, age over 40 (upright position, low-sodium diet)</b>	2.9–10.8 ng/mL/hr
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### **High values**

A high renin value can mean kidney disease, blockage of an artery leading to a kidney, Addison's disease, cirrhosis, excessive bleeding (hemorrhage), or malignant high blood pressure is present.

### **Low values**

A low renin value can mean Conn's syndrome is present.

### **What Affects the Test**

Reasons you may not be able to have the test or why the results may not be helpful include:

- Eating natural black licorice in the 2 weeks before the test.
- Taking some medicines used to treat high blood pressure.
- Taking aspirin, caffeine, estrogens, or diuretics.
- Your position (standing, sitting, or lying down) before the test is done or the time of day when the blood sample is drawn, as well as recent salt intake.
- Taking very high doses of corticosteroids.
- Being pregnant.

Aliskiren, is a first-in-class oral renin inhibitor, developed by Novartis in conjunction with the biotech company Speedel. It was approved by the US Food and Drug Administration in 2007. It is an octanamide, is the first known representative of a new class of completely non-peptide, low-molecular weight, orally active transition-state renin inhibitors. Designed through the use of molecular modeling techniques, it is a potent and specific in vitro inhibitor of human renin (IC50 in the low nanomolar range), with a

plasma half-life of  $\approx 24$  hours. Tekturna has good water solubility and low lipophilicity and is resistant to biodegradation by peptidases in the intestine, blood circulation, and the liver. It was approved by the United States FDA on 6 March 2007, and for use in Europe on 27 August 2007. Its trade name is Tekturna in the USA, and Rasilez in the UK.