

# Aldosterone

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**Abstract:** Aldosterone is a mineralocorticoid hormone, a type of hormone that is essential to life because it regulates the amounts of electrolytes in the body. The adrenal cortex, where aldosterone is produced, is part of the adrenal gland. High levels of aldosterone can cause high blood pressure, muscle cramps and weakness. Low levels may indicate disease, such as diabetes. Often, aldosterone levels vary between the sexes and may be affected by the amount of sodium in a person's diet. [Researcher. 2009;1(5):89-93]. (ISSN: 1553-9865).

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## 1. Introduction

Aldosterone is a mineralocorticoid hormone, a type of hormone that is essential to life because it regulates the amounts of electrolytes in the body. Aldosterone is secreted by the adrenal cortex and responsible for the reabsorption of sodium into the bloodstream. Aldosterone also stimulates the excretion of potassium. Aldosterone is the chief regulator of sodium, potassium, and chloride metabolism, thus controlling the body's water and electrolyte balances.

The adrenal cortex, where aldosterone is produced, is part of the adrenal gland. Aldosterone regulates sodium and potassium levels in animals, helping to maintain both blood pressure and bodily fluids. If aldosterone levels in the body are out of sync, symptoms can result.

High levels of aldosterone can cause high blood pressure, muscle cramps and weakness. Low levels may indicate disease, such as diabetes. Often, aldosterone levels vary between the sexes and may be affected by the amount of sodium in a person's diet. Women often have significantly higher levels of aldosterone when pregnant.

The hormone renin, which is produced in kidney, helps to regulate the release of aldosterone, and renin levels are often compared with aldosterone levels for diagnostic purposes. An aldosterone test may be performed to determine the cause of high or low blood potassium or of certain conditions, such as heart failure or kidney disease.

Aldosterone is an important regulator of Na<sup>+</sup> and K<sup>+</sup> transport in the distal nephron modulating the surface expression of transporters through the action of the mineralocorticoid receptor as a ligand-dependent transcription factor. Aldosterone stimulates the rapid activation of protein kinase-based signalling cascades that modulate the genomic effects of the hormone. Evidence is accumulating about the multi-factorial regulation of the epithelial sodium channel

(ENaC) by aldosterone (Thomas, McEneaney et al. 2008).

Aldosterone is a hormone that increases the reabsorption of sodium and water and the release of potassium in the kidneys. This increases blood volume and therefore, increases blood pressure. Many drugs, such as spironolactone, lower blood pressure by blocking the aldosterone receptor. Aldosterone is part of the renin-angiotensin system. Jerome Conn first described the syndrome of autonomous and excessive aldosterone secretion or "primary aldosteronism."

Aldosterone is a steroid hormone produced by the outer-section of the adrenal cortex in the adrenal gland, and acts on the distal tubules and collecting ducts of the kidney to cause the conservation of sodium, secretion of potassium, increased water retention, and increased blood pressure. The overall effect of aldosterone is to increase reabsorption of ions and water in the kidney.

Aldosterone is an adrenal hormone that regulates sodium, fluid, and potassium balance. Contrary to the historical belief, recent studies indicate that primary aldosteronism is a common cause of hypertension with a prevalence of 5-10% among general hypertensive patients. Various animal models have demonstrated that aldosterone in association with a high salt diet results in target-organ inflammation and fibrosis. Similarly, cross-sectional and observational human studies have demonstrated the association of aldosterone with development and severity of hypertension, congestive heart failure, coronary artery disease, chronic kidney disease, and metabolic syndrome. Several interventional studies have also demonstrated the beneficial effects of mineralocorticoid receptor antagonists in these disease processes, particularly hypertension, heart failure, and post myocardial infarction, further supporting the role of aldosterone in their pathogenesis (Gaddam, Pimenta et al. 2009).

When sodium intake diminishes, both the kidney and distal colon contribute directly to sodium homeostasis. In response to a diet with low amounts of sodium, the body hormonal profile changes to produce different effects on crypt-colon permeability and absorption and in the pericryptal sheath surrounding distal colonic crypts. This adaptation produces an increase in Na absorption, a decreased crypt-wall permeability, and an activation of the growth of pericryptal myofibroblasts. The separate roles of the 2 main hormones implicated in the process, aldosterone and angiotensin II, until now have been unclear. Experiments conducted on adrenalectomized rats on low- and high-sodium diets, implanted with osmotic pumps perfusing either aldosterone or angiotensin II, allow us to discriminate between the effects of these hormones. In the distal colon, aldosterone acts as a trophic agent on the myofibroblasts layer and is the key hormone controlling colonic permeability, but angiotensin II alone has no discernable direct role in the process (Cristia, Moreto et al. 2007).

Aldosterone plays a pivotal role in sodium and water homeostasis, in particular in patients with heart failure or high blood pressure. These medications, when used on top of a standard therapy, improve the outcome of patients with heart failure and are also effective in lowering blood pressure of hypertensive patients. The major risk associated with the use of these antagonists is hyperkalemia, which can be prevented in avoiding their prescription in patients with impaired renal function. Eplerenone has the advantage, compared with spironolactone, to be better tolerated in terms of "hormonal" adverse effects (Waeber 2006).

The adrenal cortex is the outer layer of the adrenal gland, a component of the endocrine system of the body which regulates and produces hormones. The inside of the adrenal gland is known as the adrenal medulla or simply medulla. The medulla and the cortex perform very different functions, and each is critical to healthy life. A variety of medical conditions can interfere with the function of the adrenal cortex, including Cushing's syndrome and Addison's disease. Using cholesterol as a base, the adrenal cortex creates a number of compounds with a variety of uses, many of which play a role in metabolism and blood chemistry.

The adrenal glands are located on top of the kidneys. The cortex is yellow in healthy individuals, and the gland itself has a star-like shape. There are three separate layers in the adrenal cortex, each of which is responsible for synthesizing different chemicals for use by the body. The cells in each layer have slightly different structures, reflecting their different functions, and the difference can clearly be

seen with the assistance of a high powered microscope.

On the outside of the adrenal cortex, the zona glomerulosa makes mineralcorticoids such as aldosterone. The next layer, the zona fasciculata, makes glucocorticoids like cortisol, while the inner layer, known as the zona reticularis, makes androgens such as testosterone. The levels of production are varied, depending on the person and his or her physical condition. Men, for example, tend to produce more testosterone than women, and this hormone plays a critical role in physical development, and people under stress make more cortisol.

Dysfunction in either area of the adrenal gland can lead to a variety of symptoms, including fatigue, weight changes, hirsutism, vomiting, nausea, specific food cravings, hypoglycemia, and low blood pressure. In some cases, multiple parts of the endocrine system are involved, creating a cascading effect as the body's overall hormonal balance is severely disrupted, and in other instances, problems occur with the adrenal gland alone. Patients who suffer from adrenal insufficiency or overproduction have a number of treatment options, depending on the cause of the condition.

When problems do emerge with the adrenal glands, doctors try to resolve the underlying cause before resorting to measures such as supplementing the body's natural level of production with specific hormones, or removing the adrenal glands so that they cannot continue to overproduce. Because many conditions can involve the adrenal gland, extensive medical testing may be required to get to the bottom of the problem.

## 2. Structure

The chemical structure of aldosterone is shown in Figure 1.

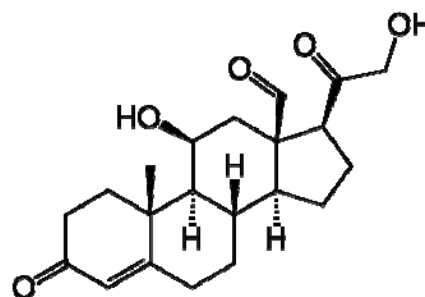


Figure 1. Chemical structure of aldosterone

Aldosterone antagonist refers to drugs which antagonise the action of aldosterone at mineralocorticoid receptors. This group of drugs is often used as adjunctive therapy, in combination with other drugs, for the management of chronic heart failure. Spironolactone, the first member of the class,

is also used in the management of hyperaldosteronism and female hirsutism. Members of this class in clinical use include: Spironolactone, Eplerenone, Canrenone. The chemical structure of aldosterone antagonists is shown in Figure 2.

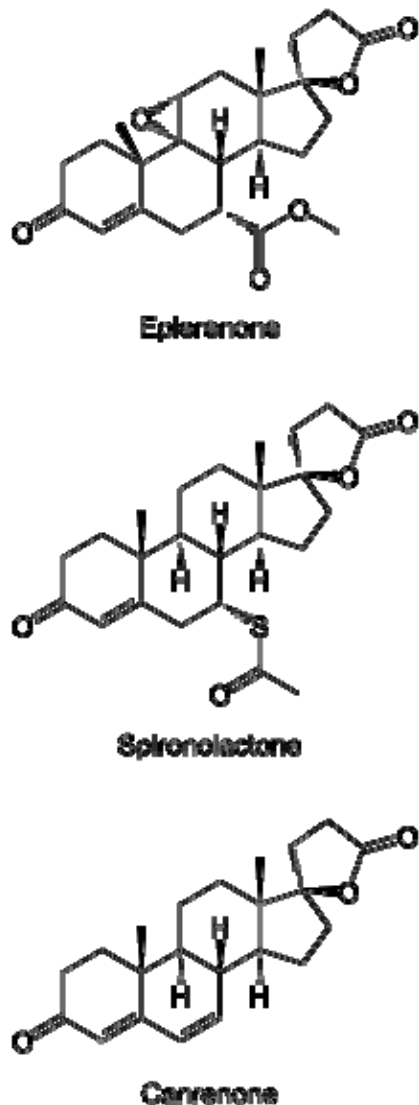


Figure 2. Chemical structure of aldosterone antagonists

Homo sapiens isolate 10 aldosterone synthase (CYP11B2) gene promoter region (187 bp DNA):

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1  gatcaatitt gcaatgaact aaatctgtgg tataaaaata
aagtctatta aaagaatcca
61  aggtccctc tcactcagc ataagataaa gtccccatcc
atfttactcc tctcagcct
121 ggagaaagga gaggccaggt cccaccacct tcaccagca
tggaccacca gtccagacc
181 cacgct

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/PCR_primers="fwd_seq:  gtgtcagggcaggggta,
rev_seq: aggcgtggggtctggact"

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Aldosterone Receptor Antagonist (34 bp DNA):

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1  gggaggtacc ttctgggcag cgggcagta ctc
(Sakamoto J, Fukumoto S, Oura T, Aldosterone
Receptor Antagonist. Takeda Chemical Industries
Ltd).

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### 3. Synthesis

The corticosteroids are synthesized from cholesterol within the adrenal cortex. Most steroidogenic reactions are catalysed by enzymes of the cytochrome P450 family. They are located within the mitochondria and require adrenodoxin as a cofactor.

Aldosterone and corticosterone share the first part of their biosynthetic pathway. The last part is either mediated by the aldosterone synthase (for aldosterone) or by the 11 $\beta$ -hydroxylase.

### 4. Aldosterone synthesis is stimulated by several factors:

- (1) Increase in the plasma concentration of Angiotensin III, a metabolite of Angiotensin II.
- (2) Increased plasma angiotensin II, ACTH, or potassium levels, which are present in proportion to plasma sodium deficiencies. The increased potassium level works to regulate aldosterone synthesis by depolarizing the cells in the zona glomerulosa, which opens the voltage-dependent calcium channels. The level of angiotensin II is regulated by angiotensin I, which is in turn regulated by the hormone renin. Potassium levels are the most sensitive stimulator of aldosterone.
- (3) The ACTH stimulation test is sometimes used to stimulate the production of aldosterone along with cortisol to determine if primary or secondary adrenal insufficiency is present.
- (4) ACTH has only a minor role in regulating aldosterone production; with hypopituitarism there is no atrophy of the zona glomerulosa.
- (5) Plasma acidosis stimulates the aldosterone synthesis.
- (6) Stretch receptors stimulates the aldosterone synthesis. If decreased blood pressure is detected, the adrenal gland is stimulated by these stretch receptors to release aldosterone, which increases sodium reabsorption from the urine, sweat and the gut. This causes increased osmolarity in the extracellular fluid which will eventually return blood pressure toward normal.
- (7) Adrenoglomerulotropin stimulates secretion of aldosterone.
- (8) The secretion of aldosterone has a diurnal rhythm.

## 5. Function

Aldosterone is the primary of several endogenous members of the class of mineralocorticoids in human. Deoxycorticosterone is another important member of this class. At the late distal tubule and collecting duct, aldosterone has three main actions:

- (1) Acting on the nuclear mineralocorticoid receptors within the principal cells of the distal tubule and the collecting duct of the kidney nephron, it increases the permeability of the apical membrane to potassium and sodium and activates the basolateral  $\text{Na}^+/\text{K}^+$  pumps, stimulating ATP hydrolysis leading to phosphorylation of the pump and a conformational change in the pump exposes the  $\text{Na}^+$  ions to the outside. The phosphorylated form of the pump has a low affinity for  $\text{Na}^+$  ions, hence reabsorbing sodium ( $\text{Na}^+$ ) ions and water into the blood, and secreting potassium ( $\text{K}^+$ ) ions into the urine. (Chlorine anions are also reabsorbed in conjunction with sodium cations to maintain the system's electrochemical balance.)
- (2) Aldosterone stimulates  $\text{H}^+$  secretion by intercalated cells in the collecting duct, regulating plasma bicarbonate levels and its acid/base balance.
- (3) Aldosterone may act on the central nervous system via the posterior pituitary gland to release vasopressin (ADH) which serves to conserve water by direct actions on renal tubular reabsorption.
- (4) Aldosterone is responsible for the reabsorption of about 2% of filtered sodium in the kidneys, which is nearly equal to the entire sodium content in human blood under normal glomerular filtration rate (GFR).

Aldosterone, most probably acting through mineralocorticoid receptors, may positively influence neurogenesis in the dentate gyrus.

## 6. Control of aldosterone release

Control of aldosterone release from the Adrenal Cortex:

- (1) The role of the renin-angiotensin system: Angiotensin is involved in regulating aldosterone and is the core regulation. Angiotensin II acts synergistically with potassium, and the potassium feedback is virtually inoperative when no angiotensin II is present. A small portion of the regulation resulting from angiotensin II must take place indirectly from decreased blood flow through the liver due to constriction of capillaries. When the blood flow decreases so does the destruction of aldosterone by liver enzymes.
- (2) The role of sympathetic nerves: The aldosterone production is also affected to one extent or

another by nervous control which integrates the inverse of carotid artery pressure, pain, posture, anxiety, fear, hostility and stress, etc. Anxiety increases aldosterone, which must have evolved because of the time delay involved in migration of aldosterone into the cell nucleus. Thus, there is an advantage to an animal anticipating a future need from interaction with a predator since too high a serum content of potassium has very adverse effects on nervous transmission.

- (3) The role of baroreceptors: Pressure in the carotid artery decreases aldosterone.
- (4) The role of the juxtaglomerular apparatus: The amount of aldosterone secreted is a direct function of the serum potassium as probably determined by sensors in the carotid artery.
- (5) The plasma concentration of sodium: Aldosterone is a function of the inverse of the sodium intake as sensed via osmotic pressure. The slope of the response of aldosterone to serum potassium is almost independent of sodium intake. Aldosterone is much increased at low sodium intakes, but the rate of increase of plasma aldosterone as potassium rises in the serum is not much lower at high sodium intakes than it is at low. Thus, the potassium is strongly regulated at all sodium intakes by aldosterone when the supply of potassium is adequate, which it usually is in primitive diets.
- (6) Adrenocorticotrophic hormone (ACTH) regulations: The pituitary peptide ACTH, also has some stimulating effect on aldosterone probably by stimulating deoxycorticosterone formation which is a precursor of aldosterone. Aldosterone is increased by blood loss, pregnancy, and possibly by other circumstances such as physical exertion, endotoxin shock, and burns.
- (7) Aldosterone feedback: Feedback by aldosterone concentration itself is of a non morphological character (that is other than changes in the cells' number or structure) and is poor so the electrolyte feedbacks predominate short term.

## 7. Location of receptors

Unlike neuroreceptors, classic steroid receptors are intracellularly located. The aldosterone/MR receptor complex binds on the DNA to specific hormone response element, which leads to gene specific transcription.

Some of the transcribed genes are crucial for transepithelial sodium transport, including the three subunits of the epithelial sodium channel, the  $\text{Na}^+/\text{K}^+$  pumps and their regulatory proteins serum and glucocorticoid-induced kinase, and channel-inducing factor respectively.

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