Aldosterone

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Aldosterone is a steroid hormone, "the main mineralocorticoid hormone",[1]:50 produced by the outer section (zona glomerulosa) of the adrenal cortex in the adrenal gland.[2][3] It plays a central role in the regulation of the plasma sodium (Na^+), the extracellular potassium (K^+) and arterial blood pressure. It does so mainly by acting on the distal tubules and collecting ducts of the nephron, increasing reabsorption and excretion of ions out of and into the the tubular fluids of the kidney, to cause the conservation of sodium, secretion of potassium, and thereby indirectly influencing water retention or loss, and influencing blood pressure and blood volume.[4] When dysregulated, aldosterone is pathogenic and contributes to the development and progression of cardiovascular and renal disease.[3] Aldosterone has exactly the opposite function of the atrial natriuretic hormone secreted by the heart.[4]

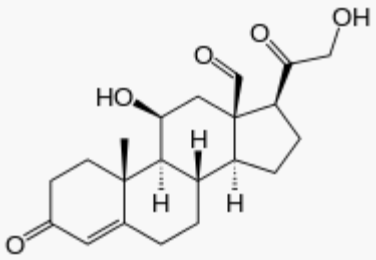
Aldosterone is part of the renin–angiotensin system. Drugs that interfere with the secretion or action of aldosterone are in use as antihypertensives, like lisinopril, which lowers blood pressure by blocking the angiotensin-converting enzyme (ACE), leading to lower aldosterone secretion. The net effect of these drugs is to reduce sodium and water retention but increase retention of potassium. Another example is spironolactone, a potassium-sparing diuretic of the steroidal spirolactone group, which decreases blood pressure by releasing fluid from the body while retaining potassium.

Aldosterone was first isolated by Simpson and Tait in 1953.[5]

Contents [hide]

1 Synthesis
  1.1 Stimulation
2 Function
3 Location of receptors
4 Control of aldosterone release from the adrenal cortex
  4.1 Major regulators
    4.1.1 The role of the renin-angiotensin system
    4.1.2 The plasma concentration of potassium
    4.1.3 ACTH
  4.2 Miscellaneous regulators
    4.2.1 The role of sympathetic nerves
    4.2.2 The role of baroreceptors
    4.2.3 The plasma concentration of sodium
  4.3 Aldosterone feedback
5 Associated clinical conditions
  5.1 Hyperaldosteronism
  5.2 Hypoaldosteronism

Aldosterone



Names	
IUPAC name	11β,21-Dihydroxy-3,20-dioxopregn-4-en-18-al
Identifiers	
CAS Number	52-39-1 ✓
ChEBI	CHEBI:27584 ✓
ChEMBL	ChEMBL273453 ✓
ChemSpider	5633 ✓
DrugBank	DB04630 ✓
IUPHAR/BPS	2872
Jmol 3D model	Interactive image
KEGG	C01780 ✓
MeSH	Aldosterone
PubChem	5839
InChI	[show]
SMILES	[show]
Properties	
Chemical formula	$C_{21}H_{28}O_5$
Molar mass	360.45 g·mol^{-1}
Pharmacology	
ATC code	H02AA01 (WHO)

Except where otherwise noted, data are given for materials in their standard state (at 25 °C [77 °F], 100 kPa).

✗ verify (what is ✓✗ ?)

Infobox references

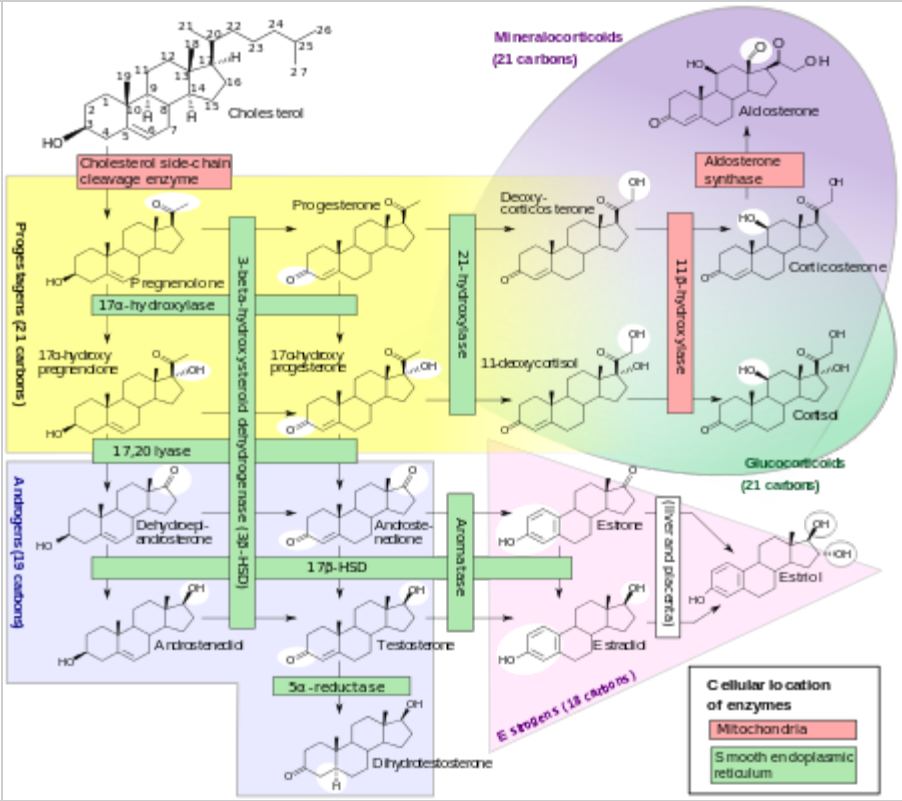
6 Additional images
7 See also
8 References
9 External links

Synthesis [edit]

The corticosteroids are synthesized from cholesterol within the zona glomerulosa of 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 (except 21-hydroxylase and 17α-hydroxylase).

Aldosterone and corticosterone share the first part of their biosynthetic pathways. The last parts are mediated either by the aldosterone synthase (for aldosterone) or by the 11β-hydroxylase (for corticosterone). These enzymes are nearly identical (they share 11β-hydroxylation and 18-hydroxylation functions), but aldosterone synthase is also able to perform an 18-oxidation. Moreover, aldosterone synthase is found within the zona glomerulosa at the outer edge of the adrenal cortex; 11β-hydroxylase is found in the zona glomerulosa and zona fasciculata.

Note: aldosterone synthase is absent in other sections of the adrenal gland.



Steroidogenesis, showing aldosterone synthesis at upper-right corner

Stimulation [edit]

Aldosterone synthesis is stimulated by several factors:

- increase in the plasma concentration of angiotensin III, a metabolite of angiotensin II
- increase in 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 renin, a hormone secreted in the kidneys.
- Serum potassium concentrations are the most potent stimulator of aldosterone secretion.
- the ACTH stimulation test, which is sometimes used to stimulate the production of aldosterone along with cortisol to determine whether primary or secondary adrenal insufficiency is present. However, ACTH has only a minor role in regulating aldosterone production; with hypopituitarism there is no atrophy of the zona glomerulosa.
- plasma acidosis
- the stretch receptors located in the atria of the heart. 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.
- adrenoglomerulotropin, a lipid factor, obtained from pineal extracts. It selectively stimulates secretion of aldosterone.[6]

The secretion of aldosterone has a diurnal rhythm.[7]

Function [edit]

Aldosterone is the primary of several endogenous members of the class of mineralocorticoids in humans. Deoxycorticosterone is another important member of this class. Aldosterone tends to promote Na^+ and water retention, and lower plasma K^+ concentration by the following mechanisms:

1. Acting on the nuclear mineralocorticoid receptors (MR) within the principal cells of the distal tubule and the collecting duct of the kidney nephron, it upregulates and activates the basolateral Na^+/K^+ pumps, which pumps three sodium ions out of the cell, into the interstitial fluid and two potassium ions into the cell from the interstitial fluid. This creates a concentration gradient which results in reabsorption of sodium (Na^+) ions and water (which follows sodium) into the blood, and secreting potassium (K^+) ions into the urine (lumen of collecting duct).
2. Aldosterone upregulates epithelial sodium channels (ENaCs) in the collecting duct and the colon, increasing apical membrane permeability for Na^+ and thus absorption.
3. Cl^- is reabsorbed in conjunction with sodium cations to maintain the system's electrochemical balance.
4. Aldosterone stimulates the secretion of K^+ into the tubular lumen.[8]
5. Aldosterone stimulates Na^+ and water reabsorption from the gut, salivary and sweat glands in exchange for K^+.
6. Aldosterone stimulates secretion of H^+ via the H+/ATPase in the intercalated cells of the cortical collecting tubules
7. Aldosterone upregulates expression of NCC in the distal convoluted tubule chronically and its activity acutely.[9]

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 rates.[10]

Aldosterone, probably acting through mineralocorticoid receptors, may positively influence neurogenesis in the dentate gyrus.[11]

Location of receptors [edit]

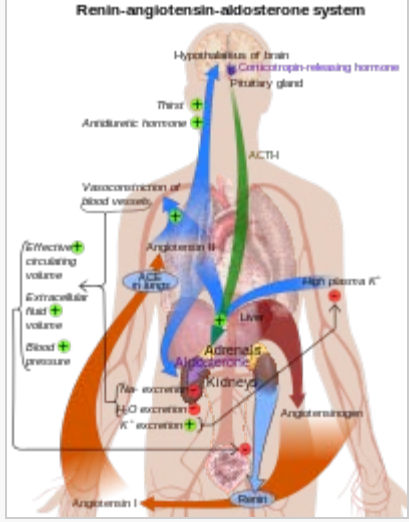
Steroid receptors are intracellular. The aldosterone mineralcorticoid receptor complex binds on the DNA to specific hormone response element, which leads to gene specific transcription.

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

The mineralcorticoid receptor is stimulated by both aldosterone and cortisol, but a mechanism protects the body from excess aldosterone receptor stimulation by glucocorticoids (such as cortisol), which happen to be present at much higher concentrations than mineralcorticoids in the healthy individual. The mechanism consists of an enzyme called 11 β-hydroxysteroid dehydrogenase (11 β-HSD). This enzyme co-localizes with intracellular adrenal steroid receptors and converts cortisol into cortisone, a relatively inactive metabolite with little affinity for the MR. Liquorice, which contains glycyrrhetinic acid, can inhibit 11 β-HSD and lead to a mineralcorticoid excess syndrome.

Control of aldosterone release from the adrenal cortex [edit]

Major regulators [edit]



The renin-angiotensin system, showing role of aldosterone between the adrenal glands and the kidneys[12]

The role of the renin-angiotensin system [edit]

Angiotensin is involved in regulating aldosterone and is the core regulation.[13] Angiotensin II acts synergistically with potassium, and the potassium feedback is virtually inoperative when no angiotensin II is present.[14] 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.[15] When the blood flow decreases so does the destruction of aldosterone by liver enzymes.

Although sustained production of aldosterone requires persistent calcium entry through low-voltage-activated Ca^{2+} channels, isolated zona glomerulosa cells are considered nonexcitable, with recorded membrane voltages that are too hyperpolarized to permit Ca^{2+} channels entry.[3] However, mouse zona glomerulosa cells within adrenal slices spontaneously generate membrane potential oscillations of low periodicity; this innate electrical excitability of zona glomerulosa cells provides a platform for the production of a recurrent Ca^{2+} channels signal that can be controlled by angiotensin II and extracellular potassium, the 2 major regulators of aldosterone production.[3] Voltage-gated Ca^{2+} channels have been detected in the zona glomerulosa of the human adrenal, which suggests that Ca^{2+} channel blockers may directly influence the adrenocortical biosynthesis of aldosterone in vivo.[16]

The plasma concentration of potassium [edit]

The amount of aldosterone secreted is a direct function of the serum potassium[17][18] as probably determined by sensors in the carotid artery.[19][20]

ACTH [edit]

ACTH, a pituitary peptide, also has some stimulating effect on aldosterone, probably by stimulating the formation of deoxycorticosterone, a precursor of aldosterone.[21] Aldosterone is increased by blood loss,[22] pregnancy,[23] and possibly by other circumstances such as physical exertion, endotoxin shock, and burns.[24][25]

Miscellaneous regulators [edit]

The role of sympathetic nerves [edit]

The aldosterone production is also affected to one extent or another by nervous control, which integrates the inverse of carotid artery pressure,[19] pain, posture,[23] and probably emotion (anxiety, fear, and hostility)[26] (including surgical stress).[27] Anxiety increases aldosterone,[26] which must have evolved because of the time delay involved in migration of aldosterone into the cell nucleus.[28] Thus, there is an advantage to an animal's anticipating a future need from interaction with a predator, since too high a serum content of potassium has very adverse effects on nervous transmission.

The role of baroreceptors [edit]

Pressure-sensitive baroreceptors are found in the vessel walls of nearly all large arteries in the thorax and neck, but are particularly plentiful in the sinuses of the carotid arteries and in the arch of the

aorta. These specialized receptors are sensitive to changes in mean arterial pressure. An increase in sensed pressure results in an increased rate of firing by the baroreceptors and a negative feedback response, lowering systemic arterial pressure. Aldosterone release causes sodium and water retention, which causes increased blood volume, and a subsequent increase in blood pressure, which is sensed by the baroreceptors.[29] To maintain normal homeostasis these receptors also detect low blood pressure or low blood volume, causing aldosterone to be released. This results in sodium retention in the kidney, leading to water retention and increased blood volume.[30]

The plasma concentration of sodium [edit]

Aldosterone is a function of the inverse of the sodium intake as sensed via osmotic pressure.[31] The slope of the response of aldosterone to serum potassium is almost independent of sodium intake.[32] 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.

Aldosterone feedback [edit]

Feedback by aldosterone concentration itself is of a nonmorphological character (that is, other than changes in the cells' number or structure) and is poor, so the electrolyte feedbacks predominate, short term.[24]

Associated clinical conditions [edit]

Hyperaldosteronism is abnormally increased levels of aldosterone, while hypoaldosteronism is abnormally decreased levels of aldosterone.

A measurement of aldosterone in blood may be termed a *plasma aldosterone concentration* (*PAC*), which may be compared to plasma renin activity (PRA) as an aldosterone-to-renin ratio.

Hyperaldosteronism [edit]

Primary aldosteronism, also known as *primary hyperaldosteronism*, is characterized by the overproduction of aldosterone by the adrenal glands,[33] when not a result of excessive renin secretion. It leads to arterial hypertension (high blood pressure) associated with hypokalemia, usually a diagnostic clue. Secondary hyperaldosteronism, on the other hand, is due to overactivity of the renin-angiotensin system.

Conn's syndrome is primary hyperaldosteronism caused by an aldosterone-producing adenoma.

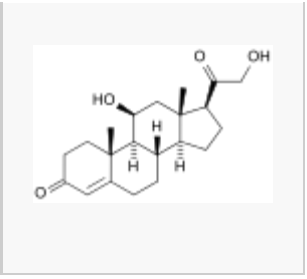
Depending on cause and other factors, hyperaldosteronism can be treated by surgery and/or medically, such as by aldosterone antagonists.

Hypoaldosteronism [edit]

An ACTH stimulation test for aldosterone can help in determining the cause of hypoaldosteronism, with a low aldosterone response indicating a primary hypoaldosteronism of the adrenals, while a large response indicating a secondary hypoaldosteronism.

Additional images [edit]

Corticosteroid biosynthetic pathway in rat



Corticosterone

See also [edit]

- Mineralocorticoid

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External links [edit]

- Aldosterone at Lab Tests Online

v · t · e ·	**Hormones**	[show]
v · t · e ·	**Endogenous steroids**	[show]
v · t · e ·	**Physiology of the kidneys and acid-base physiology**	[show]
v · t · e ·	**Mineralocorticoids and antimineralocorticoids (H02)**	[show]
v · t · e ·	**Mineralocorticoid receptor modulators**	[show]
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