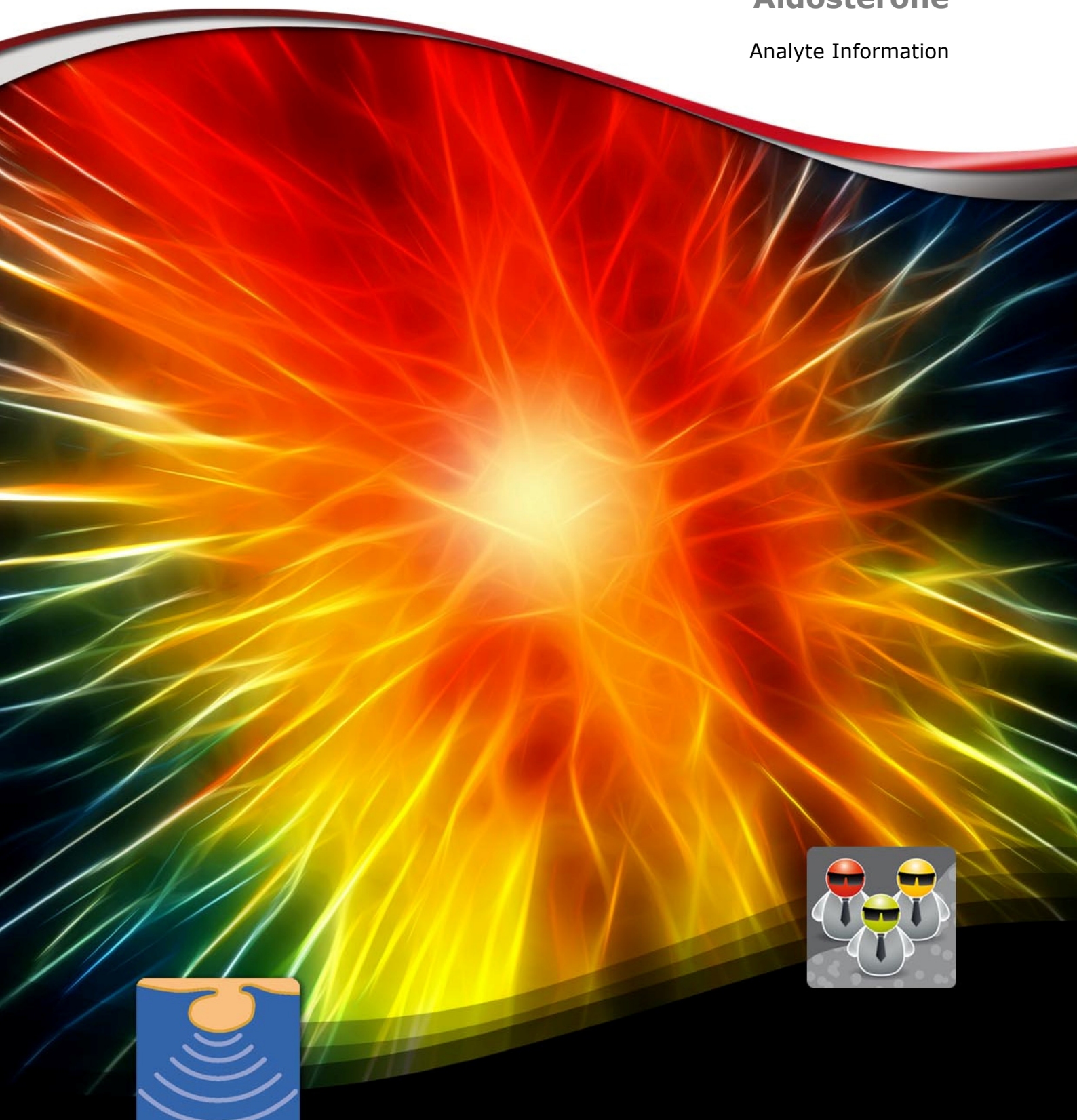




Adrenal Function

Aldosterone

Analyte Information





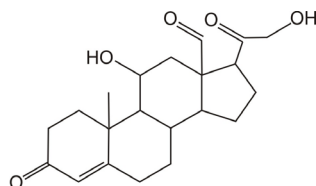
Aldosterone

Introduction

Aldosterone is a steroid hormone and is the most potent mineralocorticoid in humans. It is secreted by the adrenal cortex and regulates the body's electrolyte balance by stimulating sodium transport across cell membranes, particularly in the distal renal tubule where sodium is exchanged for hydrogen and potassium. Aldosterone is also very important in the maintenance of blood pressure and blood volume.

The chemical name of aldosterone is 11- β ,21-dihydroxy-3,20-dioxo-4-pregnen-18-al. Its molecular weight is 360.4 Da and its summary formula is $C_{21}H_{28}O_5$. The structural formula of aldosterone is shown in Fig.1.

Fig.1 –The structural formula of aldosterone



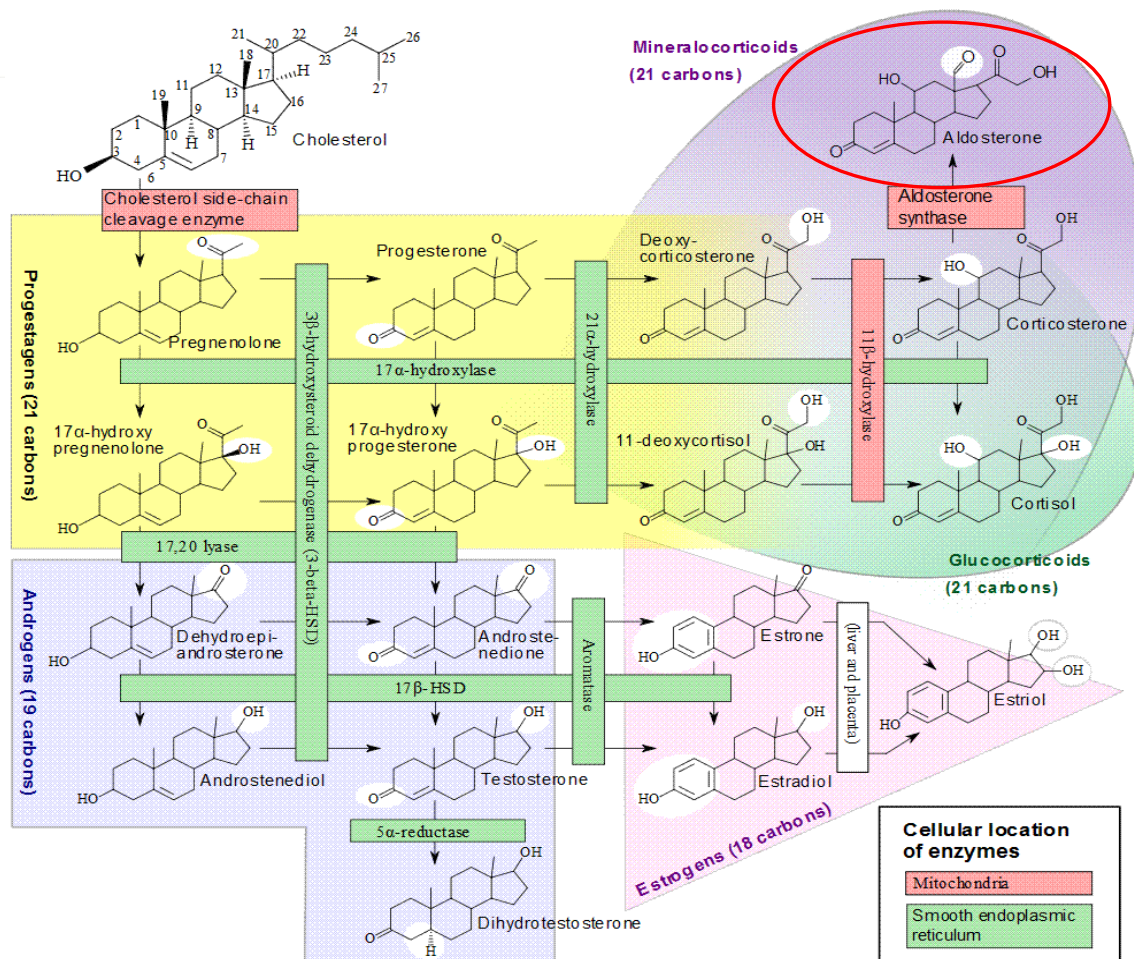
This chemical compound is also known as 18-oxocorticosterone, aldocorten, aldocortin, and electrocortin.

Biosynthesis

As with other steroid hormones, aldosterone is synthesized from cholesterol via a series of enzyme-mediated steps¹ (Fig.2); like other corticosteroids, this synthesis occurs in the adrenal cortex. Much of aldosterone's biosynthetic pathway is identical to that of corticosterone. It begins with the conversion of cholesterol to pregnenolone under stimulation of adrenocorticotropic hormone (ACTH)¹, and continues until the final corticosterone molecule is converted to aldosterone via aldosterone synthase, which occurs in the zona glomerulosa at the outer edge of the adrenal cortex.



Fig.2 – Steroidogenesis



Metabolism

Average aldosterone production is about 50-250 µg per day. Aldosterone circulates in blood weakly bound to albumin, or more tightly bound to transcortine (cortisol-binding globulin – CBG) or the specific binding protein (aldosterone-binding globulin – ABG). The principal site of catabolism is the liver; 90% of aldosterone is cleared from the blood during a single passage. Aldosterone is inactivated by reduction to tetrahydro-derivatives, and is then conjugated to glucuronic acid and excreted in urine.



Physiological Function

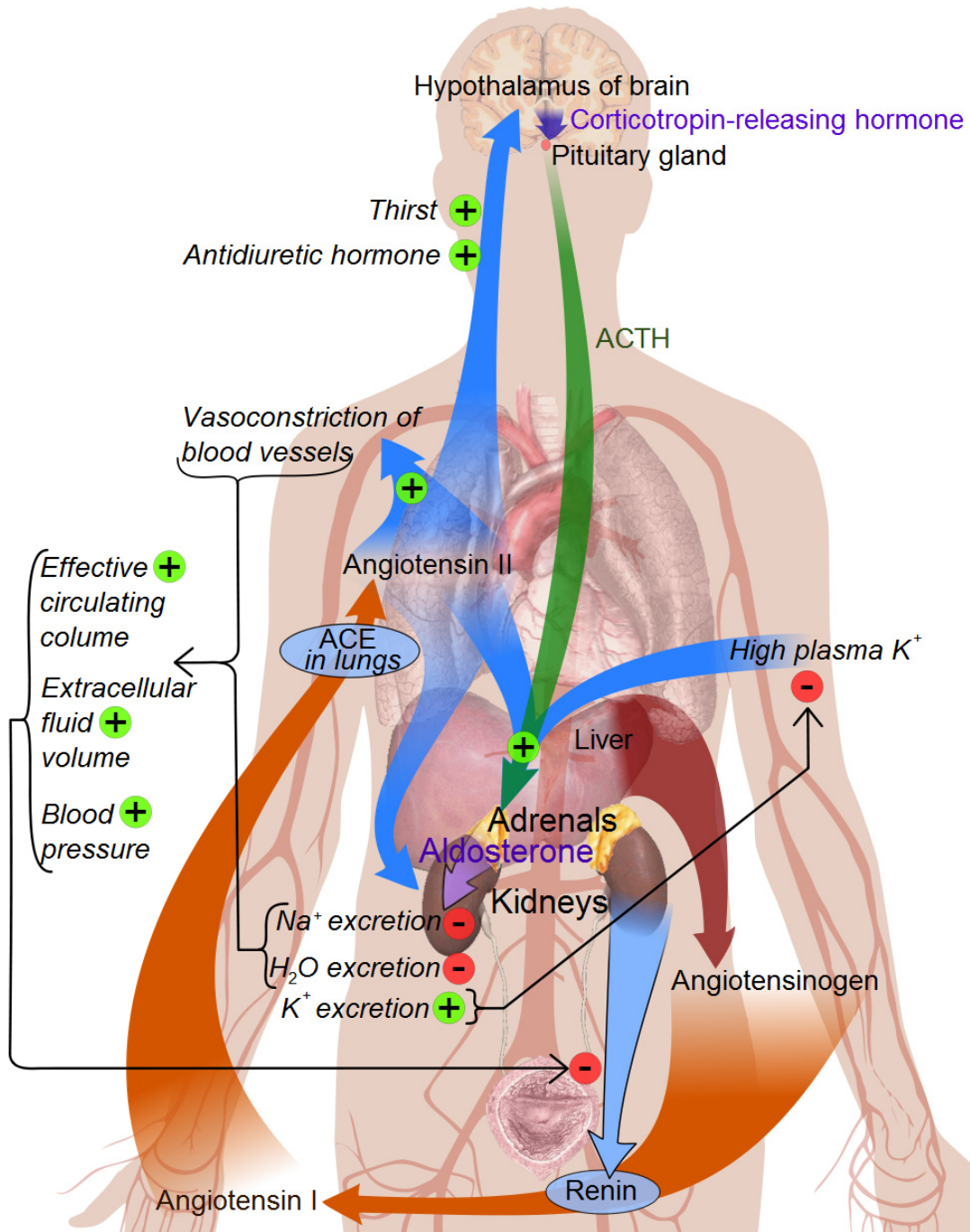
Aldosterone secretion appears to be stimulated primarily via the renin-angiotensin-aldosterone system. Decreased plasma volume and renal perfusion or decreased plasma sodium chloride concentration leads to an increase in renin secretion and production of angiotensin I, followed by increased production of angiotensin II and stimulation of aldosterone secretion. Elevated plasma potassium concentrations are also a strong stimulus for aldosterone production, although this is partially countered by the potassium inhibition associated with renin release²⁻⁵.

Aldosterone's main function is to stimulate renal tubular sodium and chloride reabsorption, primarily within collecting ducts²⁻⁵. Other important renal activity includes facilitating the excretion of potassium and hydrogen (acid) in urine. Similar effects on transmembrane sodium and hydrogen transport have been observed in other tissues, including lymphocytes, the brain, and arterial smooth muscle⁶.

The renin-angiotensin-aldosterone system (RAS or RAAS) is the hormone system that regulates blood pressure and water (fluid) balance. Sodium excretion and extracellular fluid volume are inversely related to plasma renin activity (PRA) and plasma aldosterone concentrations⁷.



Fig.3 - The renin-angiotensin system, showing role of aldosterone in adrenal glands and kidneys⁸.





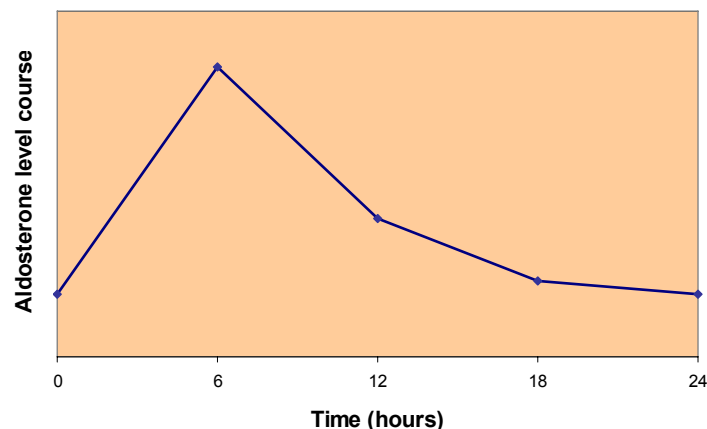
When blood volume is low, the kidneys secrete renin. Renin stimulates the production of angiotensin I, which is converted to angiotensin II by ACE (angiotensin converting enzyme). Angiotensin II causes blood vessels to constrict, resulting in increased blood pressure. Angiotensin II also stimulates the secretion of aldosterone from the adrenal cortex. Aldosterone causes the tubules of the kidneys to increase reabsorption of sodium and water into the blood. This increases the volume of fluid in the body, which also acts to increase blood pressure. Excessive renin-angiotensin-aldosterone system activity will result in high blood pressure.

Levels

Aldosterone levels vary with posture and salt intake. Supine aldosterone values are on average 50% lower than upright values. Sodium-depleted subjects have significantly elevated serum aldosterone levels, which may be several times higher than normal reference range limits.

Overall aldosterone levels follow a diurnal rhythm, with peak levels in the early morning⁹. Late afternoon levels may be up to 30% lower than early-morning values (Fig.4).

Fig.4 – Diurnal aldosterone level course¹⁰



In general, levels tend to decline with age^{5,11}.



A large number of factors and conditions influence aldosterone production and secretion. They are summarized in the following tables.

Factors stimulating the production and secretion of aldosterone include¹²:



- upright posture
- thermal stress
- sodium depletion
- kalium depletion
- bleeding
- long-term starvation
- dehydration
- oral contraceptives
- gestation
- in women in the mid and late luteal phases of the menstrual cycle
- drug treatment (laxatives, diuretics, spironolactone)

Factors inhibiting the production and secretion of aldosterone¹²:



- advanced age
- prolonged heparin therapy
- licorice intake
- saline intake
- acute alcoholic intoxication
- ACE (angiotensin converting enzyme) inhibitors (captopril, enalapril, lisinopril)
- drug treatment (deoxycorticosterone, indomethacin, saralasin)

Sample reference intervals for aldosterone levels¹² are listed in Table 1. These are strictly for informational purposes, as appropriate reference levels vary according the assay used.



Table 1 – Typical aldosterone levels

Specimen	Reference interval (ng/dL)
Cord blood:	40 - 200
Premature infants:	19 - 141
Full-term infants	
3 days:	7-184
1 week:	5 - 175
1-12 months:	5 - 90
Children	
1-2 years:	7 - 54
2-10 years	
(supine):	3-35
(upright):	5-80
10-15 years	
(supine):	2-22
(upright):	4-48
Adults	
(supine):	3-16
(upright):	7-30
Adrenal vein:	200-800

Equation for the conversion of the units: 1 ng/dL = 0.0278 nmol/L

Urine aldosterone levels in the urine may also be monitored. Samples are usually collected over the course of 24 hours. This is especially suitable for people with similar aldosterone concentrations in both upright and supine positions^{5,13,14}.

An aldosterone stimulation test may be given after sodium restriction, or an aldosterone suppression test after saline infusion. These tests are used, e.g., in the evaluation of patients with primary aldosteronism.



Diagnostic utility – clinical significance of aldosterone determination

The symptom most closely related to aldosterone production and the Renin–Angiotensin–Aldosterone–System (RAS) is hypertension. In hypokalemic states, determination of RAS activity is of great importance as well.

Endocrine hypertension frequently occurs in cases of primary adrenal disorders (pheochromocytoma, primary hyperaldosteronism, deoxycorticosterone or cortisol producing tumors), pituitary gland tumors producing adrenocorticotrophic hormone (ACTH), and renal disorders (renin producing tumors, renovascular disease, some types of tubulopathies).

Arterial hypertension can occur in cases of endocrine disorders (acromegaly, thyrotoxicosis, hypothyreosis, hyperparathyreosis, hyperinsulinism).

A wide scale of tests is used in diagnosis. These various combinations are summarized in tables 1-3.

Mineralocorticoid hypertension

This is hypertension due to the effects of mineralocorticoid hormones. Mechanisms by which these hormones lead to hypertension include:

- Primary excess of mineralocorticoids
- Syndromes with secondary mineralocorticoids excess
- Other hypertension syndromes with pseudohyperaldosteronism



Primary excess of mineralocorticoids

The disorders are characterized by hypertension, hypokalemia, RAS suppression and normal or subnormal cortisol production. The biochemical findings for appropriate markers connected with the disorders of interest are summarised in Table 1¹⁵.

Table 1: Primary hypermineralocorticoidism - Biochemical findings

	Plasma Na+	Plasma K+	ALD	Other MCH	Renin	Cort	ACTH	Hematocrit	BUN/CR
Adenom producing aldosterone	N/↑	↓	↑↑	↑	↓↓	N	N	↓	N
Carcinom producing aldosterone	↑	↓	↑↑	↑↑	↓↓	N/↑	N/↓	↓	N
Hyperplasia:									
Idiopathic hyperaldosteronism	N	↓	↑	N	↓	N	N	N/↓	N
Undetermined hyperaldosteronism	N	N/↓	↑	N	↓	N	N	N/↓	N
Hyperaldosteronism curable by glucocorticoids	N	↓	↑	N	↓	N	N	N/↓	N
Primary hyperplasia	N/↑	↓	↑↑	↑	↓↓	N	N	↓	N
Defective 11β-hydroxylase	N	N/↓	↓	↑	N/↓	N/↓	↑	N/↓	N
Defective 17α-hydroxylase	N/↑	↓	↓	↑↑	↓↓	↓	↑	N/↓	N

ALD	Aldosterone	↑	Increase
MCH	Mineralocorticoid hormones	↓	Decrease
Cort	Cortisol	↑↑	Significant increase
ACTH	Adrenocorticotrophic hormone	↓↓	Significant decrease
BUN	Plasmatic urea nitrogen	N	Normal
CR	Creatinin		



Syndroms with secondary excess of mineralocorticoids

The activation of the zona glomerulosa of the adrenal gland due to RAS activity is associated with various states characterized by aldosterone overproduction, e.g., renal disorders connected with salt loss, dehydration, cirrhosis, heart failure and decrease of intravascular volume, and overusage of laxatives or diuretics. These cases are rarely accompanied by hypertension. In contrast hypertension is typical for disorders with direct renin overproduction, e.g., renovascular hypertension and renin-producing tumors. The biochemical findings for appropriate markers connected with the disorders of interest are summarised in Table 2¹⁵.

Table 2: Secondary hypermineralocorticoidism - Biochemical findings

	Plasma Na+	Plasma K+	ALD	Other MCH	Renin	Cort	ACTH	Hemato-crit	BUN/CR
Renovascular hypertension	N/↑	N/↓	↑	N	↑	N	N	↑	N/↑
Cancer producing renin	N/↑	↓	↑↑	N	↑↑	N	N	↑	N
Accelerated hypertension	N	N/↓	↑	N	↑	N	N	N/↑	N/↑
Estrogen treatment	N	N/↓	↑	N	N/↑	N/↑	N	N/↓	N
Cushing's syndrome	N	N/↓	N/↓		N	↑	N/↑	N	N

ALD	Aldosterone	↑	Increase
MCH	Mineralocorticoid hormones	↓	Decrease
Cort	Cortisol	↑↑	Significant increase
ACTH	Adrenocorticotrophic hormone	↓↓	Significant decrease
BUN	Plasmatic urea nitrogen	N	Normal
CR	Creatinin		



Other hypertension syndromes with pseudohyperaldosteronism

Secondary mineralocorticoid deficiency (pseudohyperaldosteronism) comprises a heterogeneous group of disorders with abnormally low mineralocorticoid production due to suppressed renin production.

Hypertension, hypokalemia and metabolic alkalosis are the usual clinical manifestations of decreased renin production. This is due to increased sodium retention and by volume expansion caused by exogenous mineralocorticoids, mineralocorticoid-like substances or by renal tubular defect.

If renin production is suppressed and thus insufficient to stimulate production of mineralocorticoids, sodium loss, hyperkalemia and metabolic acidosis occur.

The biochemical findings for appropriate markers connected with the disorders of interest are summarised in Table 3¹⁵.

Table 3: Pseudohyperaldosteronism - Biochemical findings

	Plasma Na ⁺	Plasma K ⁺	ALD	Other MCH	Renin	Cort	ACTH	Hematocrit	BUN/CR
Pseudohyperaldosteronism (Liddle's syndrome)	N/↑	↓	↓	N/↓	↓	N	N	↓	N
Arnold-Healy-Gordon's syndrome	N/↑	↑	↓	N/↓	↓	N	N	N/↓	N
Treatment with synthetic MCH	N/↑	↓	↓	N/↓	↓	N	N	↓	N
Licorice digestion	N/↑	↓	↓	N/↓	↓	N	N	↓	N
Primary cortisol resistance	N/↑	↓	N/↓	↑	N/↓	↑	↑	N/↓	N

ALD	Aldosterone	↑	Increase
MCH	Mineralocorticoid hormones	↓	Decrease
Cort	Cortisol	↑↑	Significant increase
ACTH	Adrenocorticotrophic hormone	↓↓	Significant decrease
BUN	Plasmatic urea nitrogen	N	Normal
CR	Creatinin		



Diagnostic utility – Summary of practical applications

When to measure aldosterone

In cases of one or more of the following situations:

- Diastolic blood exceeds 110 mm Hg (hypertension of renal origin)
- Hypokalemia: less than 3.8 mmol/L (secondary hyperaldosteronism, primary mineralocorticism)
- Insufficient response to antihypertensive treatment
- Suspected adrenal deficiency

Aldosterone values and healthy status – overview¹⁶

Aldosterone level determination is used in the diagnosis of the following disorders:

↑ ALDOSTERONE INCREASE

Primary aldosteronism

- aldosterone secreting adenoma (Conn's syndrome)
- pseudoprimary aldosteronism (bilateral adrenal hyperplasia)

Secondary aldosteronism

- laxative abuse
- diuretic abuse
- cardiac failure
- cirrhosis of the liver with ascites formation
- nephrotic syndrome
- idiopathic cyclic edema
- Bartter's syndrome
- hypovolemia due to the hemorrhage and transudation
- renal juxtaglomerular hyperplasia with potassium wastage and retarded growth
- renin-producing hemangiopericytoma of the kidney
- renal hypertension during malignant phase
- chronic obstructive lung disease

↓ ALDOSTERONE DECREASE

Without hypertension

- Addison's disease
- isolated aldosterone deficiency
- hypoaldosteronism due to renin deficiency

With hypertension

- excessive secretion of deoxycorticosterone
- excessive secretion of 18-hydroxydeoxycorticosterone
- Turner's syndrome
- diabetes mellitus



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