Accepted Manuscript online: 2023-03-14 Article published online: 2023-05-08

An Abbreviated History of Aldosterone Metabolism, Current and Future Challenges

Authors
Celso E Gomez-Sanchez, Elise P Gomez-Sanchez

Affiliations
G.V. (Sonny) Montgomery VA Medical Center and Department of Pharmacology and Toxicology, University of Mississippi Medical Center, Jackson, MS, United States of America

Key words
GH Adrenal gland, Hormones, aldosterone, primary aldosteronism

received 16.01.2023
revised 02.03.2023
accepted 09.03.2023
online publiziert 08.05.2023

Bibliography
Exp Clin Endocrinol Diabetes 2023; 131: 386–393
DOI 10.1055/a-2054-1062
ISSN 0947-7349
© 2023. Thieme. All rights reserved.
Georg Thieme Verlag, Rüdigerstraße 14,
70469 Stuttgart, Germany

Correspondence
Celso E. Gomez-Sanchez
G.V. (Sonny) Montgomery VA Medical Center
1500 E. Woodrow Wilson Dr. Jackson, MS
39216
United States of America
Tel.: + 1 601 368 3844
Cgomez-sanchez@umc.edu

ABSTRACT

The initial isolation of adrenal steroids from large quantities of animal adrenals resulted in an amorphous fraction resistant to crystallization and identification and had potent effects on electrolyte transport. Aldosterone was eventually isolated and identified in the fraction and was soon shown to cause hypertension when in excess. The autonomous and excessive production of aldosterone, primary aldosteronism, is the most common cause of secondary hypertension. Aldosterone is metabolized in the liver and kidney, and its metabolites are conjugated with glucuronic acid for excretion. The most common liver metabolite is 3α,5β-tetrahydroaldosterone-3-glucuronide, while that of the kidney is aldosterone-18-oxo-glucuronide. In terms of their value, especially the aldosterone-18-oxo-glucuronide, is commonly used for the diagnosis of primary aldosteronism because they provide an integrated value of the total daily production of aldosterone. Conversion of aldosterone to 18-oxo-glucuronide is impeded by drugs, like some common non-steroidal anti-inflammatory drugs that compete for UDP-glucuronosyltransferase-2B7, the most important glucuronosyltransferase for aldosterone metabolism. Tetrahydroaldosterone is the most abundant metabolite and the most reliable for the diagnosis of primary aldosteronism, but it is not commonly measured.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

Introduction

History of adrenal discovery and function

A comprehensive history of the adrenal gland was recently published [1]. The anatomy of the human adrenal gland was first described by Bartolomeo Eustachi (1520–1574) in his book Opuscola Anatomica, published in 1564, with the first 8 plates of 47 engraved copper plates comprising anatomical illustrations by the Roman artist Pier Matteo Pini. A detailed drawing of the anatomy of the kidney clearly depicts the suprarenal (adrenal) glands. The plates remained in the Vatican library for 150 years until Pope Clement XI gave them to his personal physician, Giovanni M. Lancisi, who published them in 1714 as Tabulae Anatomicae Clarissimi viri Bartholomaei Eustacci. The physiological importance of the adrenal gland was first reported in 1855 by Thomas Addison, who described hyperpigmentation, anemia, general languor, debility, feebleness of the heart's action, and gastric irritability associated with diseased suprarenal capsules [2]. Soon thereafter, Charles-Edouard Brown-Sequard reported that adrenalectomy in dogs led to death, indicating that adrenal glands were essential for life [1]. The search for an adrenal secretion led to the isolation and crystallization of epinephrine by Takamine [3]; however, functions of the adrenal medulla and cortex were quickly recognized to be distinct, and that lipoidal extracts of the adrenal were required to sustain the life of adrenalectomized animals [4, 5].

Isolation and chemical characterization of adrenal cortical steroids

The isolation of steroid hormones and chemical characterization of their structures were performed by many groups during the 1930–1940s [1]. Reichstein isolated and determined the structure of 28 adrenal corticoids, of which only 5 had biological activity [6]. Among these was cortisone, also isolated at Mayo Clinic by Kendall, who first demonstrated its biological activity [7]. Desoxycorticosterone (deoxycorticosterone or DOC) was first isolated and synthesized by Reichstein [8] and was shown to be useful in the treatment of Addison's disease [9]. Under low-stress conditions, mineralocorticoids like DOC were more potent in keeping adrenalectomized animals alive; however, under stress conditions, glucocorticoids like cortisol were more effective. However, DOC production was found to be too low [1] to explain sodium retention and edema in patients with nephrosis and congestive heart failure, so the search for another mineralocorticoid continued.

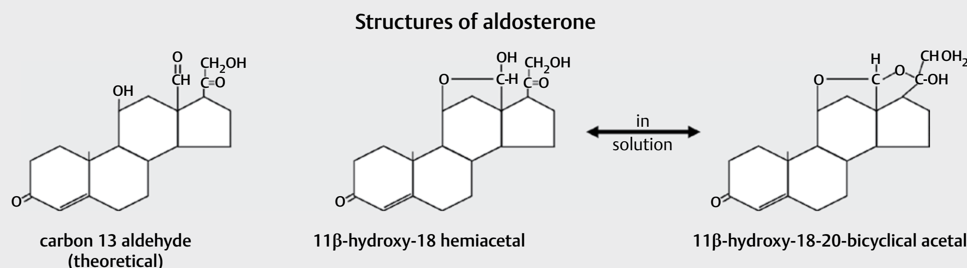
Steroids were initially isolated from large quantities of beef or hog adrenals by extraction with organic solvents, followed by various chemical and physical separatory processes, and finally by crystallization. During isolation, a significant amount of salt-retaining activity remained in a residue called the amorphous fraction which could not be crystallized [10]. The use of large doses of cortisone in clinical applications in the late 1940s and early 1950s demonstrated that it had both glucocorticoid and mineralocorticoid properties, leading several prominent steroid researchers to propose the unitarian hypothesis that cortisol was the only adrenal hormone responsible for both glucocorticoid and mineralocorticoid activity, and subsequently, also for the adrenal steroid-mediated hypertension [11, 12]. Demonstration that cortisone was efficiently converted to cortisol in extra-adrenal tissues supported this premise [13]. Others believed that a yet undiscovered steroid or mixture of steroids was responsible for the mineralocorticoid properties of the amorphous fraction and that discrepancies between results from different studies were due to different bioassays employed to determine biological effects. Kendall used the Ingle work test, which is particularly suited for detecting glucocorticoids but not mineralocorticoids, while Reichstein used the Everse and de Fremery assay, which was more specific for mineralocorticoid activity [14]. The isolation of aldosterone by the Reichstein laboratory was probably delayed by the need to acetylate the steroids prior to purification using alumina columns and because, though most 21-monoacetylate steroids are very active, the diacetate of aldosterone is completely inactive.

The development of bioassays based on the direct action of mineralocorticoids on electrolyte metabolism in the late 1940s simplified the determination of mineralocorticoid activity [15]. The use of radioactive sodium (Na^{24}) and potassium (K^{42}) injections before the collection of urine to determine the mineralocorticoid activity of the test substances increased the sensitivity of early flame photometric measurements of these analytes [16], but the use of radioisotopes became unnecessary with the development of more sensitive flame photometers [17]. A crucial development for the purification of the amorphous fraction was the development of paper partition chromatography using the Zaffaroni system of a stationary phase of propylene glycol saturated with toluene and a mobile phase of toluene saturated with the stationary phase. The biologically active mineralocorticoid migrated at the same speed as cortisone when the system was run for 3 days, but was only partially separated after 7 days [18, 19]. The Bush system, in which the stationary phase was methanol and water saturated with benzene and the mobile phase was benzene saturated with the stationary phase (Bush B5 system), clearly separated cortisone from the mineralocorticoid active fraction [18, 20]. Material extracted from adrenal blood migrated at the same speed as the fraction isolated from beef adrenals and had been called electrocortin, later renamed aldosterone [18]. The purified fraction retained its biological function upon partial acetylation but was inactivated by extensive acetylation; its function was restored by gentle hydrolysis [21].

At the same time, John Luetscher at Stanford University was working on the identification of a salt-retaining hormone in the urine of patients with nephrotic syndrome. He initially believed it was a vasopressin-like substance, but discovered that it was very similar and more potent than DOC [22]. His attempts to purify and characterize the substance were initially unsuccessful. After the structure of aldosterone was published, the Luetscher group was able to isolate and crystalize aldosterone from human urine and demonstrate that it was identical to that isolated from beef adrenals [23]. His group's method of isolating the biologically active aldosterone from urine acidified to pH 1 to hydrolyze it became standard for measuring urinary aldosterone as it substantially increased the amount isolated [23–25].

The original identification of the structure of aldosterone used microchemical methods, including the Bush soda fluorescent method specific for the 4-en-3one group, rapid reaction with tetrazolium, the release of formaldehyde after oxidation with bismuthate to detect the 20,21-ketols, and acetylation with [^{14}C]-acetic anhydride showing that electrocortin had two acetylatable hydroxy groups, one at position 21 and the other that was initially unclear [21]. There were several possibilities for the position of the second hydroxy group. Reichstein, who had isolated 50 mg of the steroid, demonstrated that oxidation of the steroid yielded a γ-lactone [21, 26–28], suggesting the presence of an aldehyde at position 18, which, due to the proximity of the 11β-hydroxy group, forms a hemiacetal and a bicyclic acetal [21, 28, 29]. Once X-ray crystallography and NMR became available, it was shown that aldosterone in crystal form is the bicyclic acetal [30] (▶ **Fig 1**), while in solution, it is a mixture of the readily interconverted hemiacetal and bicyclic acetal forms [29, 31]. The parent structure of an aldehyde in position 13 drawn in many publications has never been confirmed in solution or solid state due to the very high reactivity of the -CHO group at C-13 with the 11β-hydroxy (forming a hemiacetal) and the 11β-hydroxy, the -CHO group at C-13, and 20-keto which form the more stable bicyclic acetal. The synthesis of aldosterone made it available for studies and the design of multiple methods for its measurement [32–34]. A recent quantitative NMR study of aldosterone samples from two commercial sources that were at least 95 % pure by liquid chromatography with tandem mass spectrometric (LC-MS-MS) demonstrated by quantitative ^{1}HNMR that in the purest sample, the diastereomers are in a tautomeric equilibrium of the bicyclic acetal 18*R*,20*S* and 18*S*,20-oxo in a proportion of 3:4 [29]. ^{1}HNMR showed that this sample was 93.8 % pure, while the other was only 81.85 % pure. The contaminants present included dimers, aldosterone acetal, and aldosterone-γ-

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.



▶ **Fig. 1** Structures of aldosterone as the theoretical carbon 13 aldehyde of aldosterone and the two acetals found in solution,11β-hydroxy-18 hemiacetal and 11β-hydroxy-18–20-bicyclic acetal of aldosterone.

lactone. The use of different sources of aldosterone as standards for its quantification has significant repercussions in precision and reproducibility between laboratories [29].

Metabolism of aldosterone

Aldosterone is synthesized in the zona glomerulosa of the adrenal [35] and released upon stimulation by angiotensin II, potassium, and acutely by ACTH and other peptides [36, 37]. Aldosterone secretion rates in the human were initially measured by the isotope dilution method using [^{3}H]-aldosterone produced by incubating [^{3}H]-progesterone with adrenal glands, then purified [38]. A known amount and specific activity of [^{3}H]-aldosterone was administered intravenously in humans, then an aldosterone metabolite (tetrahydroaldosterone or aldosterone-18-oxo-glucuronide) was isolated from the urine and its specific activity measured. The secretion rate was calculated by comparing the specific activity of the metabolite compared to the specific activity of the infused aldosterone [39, 40]. The distribution volume and turnover rate of aldosterone are greater than those of cortisol [41, 42] because cortisol is extensively and tightly bound to corticosteroid-binding protein, whereas aldosterone is weakly bound.

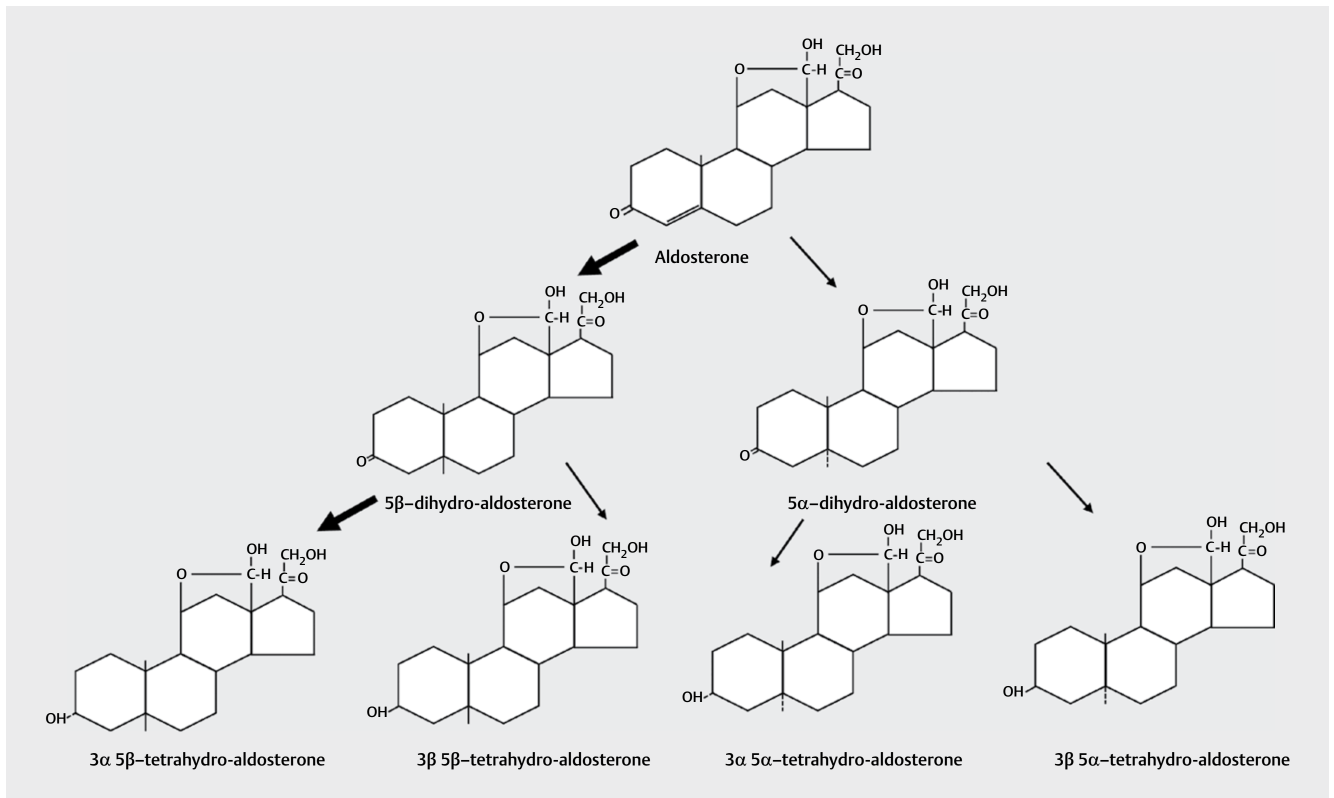
Studies of the metabolic clearance rate measured after the continuous infusion of [^{3}H]- aldosterone demonstrated that most aldosterone was cleared by the liver, with a small portion cleared by the kidney and even less by other tissues [43]. The primary catabolic process is the reduction of the 4–5-double bond, producing both the 5β- and 5α- reduced dihydro steroid and further reduction of the 3-ketone to a 3α- or 3β-hydroxy group (▶ **Fig 2**). The most abundant metabolite is 3α,5β-tetrahydroaldosterone [44], corresponding to about 30–50 % of the secretory rate of aldosterone [45, 46]. Smaller amounts of 3α,5α-tetrahydroaldosterone and 3β,5β-tetrahydroaldosterone are also excreted in the urine. 3α,5β-tetrahydroaldosterone is also the main metabolite when aldosterone is incubated with a liver homogenate. The tetrahydroaldosterones are conjugated with glucuronic acid for excretion, as described below.

At the time aldosterone was isolated, the techniques available for the identification of steroid metabolites required large amounts of steroid. Aldosterone metabolites were often isolated from the urine of individuals who consumed a large amount of aldosterone, 100–200 mg (considering that only about 100 μg are normally secreted by the adrenal), that included a known amount of tritiated aldosterone to follow the purification [47–49]. Among the several other metabolites isolated was one described as 11β:18(S),18:.20α−diepoxy-5β-pregnan-3α-ol [48] and called the Kelly M1 metabolite. It was found in normal individuals and in higher concentrations in patients with 21-hydroxylase deficiency [50]. Aldosterone in the gut is deoxygenated to 21-deoxyaldosterone and other metabolites by gut bacteria [51] and is probably the origin of the Kelly M-1 metabolite. Acid hydrolysis of urine for the measurement of aldosterone can lead to significant modification of the aldosterone structure with the formation of 18,21-anhydroaldsterone, aldosterone-γ-etiolactone, and dimers of aldosterone [52, 53]. In addition to 3β,5β-tetrahydroaldosterone, incubation of aldosterone with liver homogenates produces other metabolic products, including 2α-hydroxyaldosterone [54], 6β-hydroxyaldosterone [55], and others [56]. Some metabolites of aldosterone have similar, albeit weaker, electrolyte-modulating activities than aldosterone [57, 58]. Interestingly, the reduction at the 3 and 5 positions can be modified by changes in sodium intake; a low sodium intake increases the proportion of 5α-dihydroaldosterone, and a high sodium diet increases the proportion of 5β-dihydroaldosterone [59]. The 5α-reduced aldosterone is a more potent promoter of sodium retention than the 5β-reduced aldosterone [60].

Other metabolites of aldosterone

A small amount of aldosterone-21-sulfate, corresponding to approximately 2.5 % of the adrenal production of aldosterone, was found in the urine [61]. Methods for the synthesis of aldosterone-21-sulfate and its separation from the aldosterone-18-oxo-glucuronide in the urine were designed, allowing the measurement of its excretion by hydrolyzing aldosterone-21-sulfate with sulfatase, then determining the free steroid by conventional double isotope technique [61]. Excretion of aldosterone-21-sulfate in five normal subjects on a normal sodium diet was 2.09 + /−0.64 μg/24 h; one patient with primary aldosteronism had six times greater excretion [61]. Further studies demonstrated that aldosterone-21-sulfate concentration in adrenal vein blood is higher than that in peripheral blood and about one-tenth that of aldosterone [62]. Its biological activity using the adrenalectomized rat bioassay is approximately 1 % that of aldosterone [62]. Aldosterone incubated with aldosterone-producing adenomas was converted into a water-soluble compound shown to be aldosterone-21-sulfate [62].

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.



▶ **Fig. 2** Metabolic products of aldosterone metabolism.

The urinary measurement of aldosterone-3-oxo-glucuronide (urinary aldosterone), 3α,5β-tetrahydroaldosterone, and urinary free aldosterone have been used for diagnostic purposes for aldosterone disorders of overproduction and less often for diagnosing underproduction. Multiple other metabolites of aldosterone have been described, but most correspond to a very low proportion of the metabolized aldosterone and have not been found to have physiological or diagnostic consequences. The far less abundant metabolites were usually found when large amounts of aldosterone (100–200 mg or about 1,000 times the average production rate of aldosterone) were administered orally and the urine collected for isolation and determination of the metabolites [40, 44, 47–49].

Aldosterone-18-oxo-glucuronide (urinary aldosterone or acid-labeled metabolite)

Luetscher's group was the first to report that acidification of the urine significantly increased the mineralocorticoid activity of its extract, later identified as aldosterone [22, 24]. Urine from normal subjects extracted at pH 6.5 yielded only trace amounts of aldosterone, but upon keeping the urine for a day at pH 1, a far larger amount [22, 24, 63, 64] was isolated. Further determination of the nature of the conjugate of urinary aldosterone showed that glucuronidase-treated urine also yielded minimal amounts of aldosterone. The reaction of the isolated urinary aldosterone with napthoresorcinol confirmed that the compound was a conjugate of glucuronic acid [64]. It was originally referred to as a 3-oxo conjugate or acid-labile conjugate. Studies by Pasqualini et al. [65] and Underwood and Tait [66] suggested that it was an 18-oxo-glucuronide. Studies indicated that about 7.8 % of the secretion of aldosterone is converted to this glucuronide in normal subjects, with a range of 5 to 15 % [66, 67]. Factors involved in the measurement of urinary aldosterone depend on the adequacy of the urine collection, the standardization of the conditions for acid, including pH, temperature, and duration of the exposure to the acid, due to the competition between the hydrolysis of the conjugate and acid-induced degradation of aldosterone [64, 68, 69], and the assay for the measurement of aldosterone [69–71]. The proportion of aldosterone excretion as the aldosterone-18-oxoglucuronide in women with a standard sodium intake is greater in pregnancy [72]. Measurement of urinary aldosterone, which is mostly 18-oxo-glucuronide, on a high sodium diet is one of the recommended confirmatory tests for primary aldosteronism [73] and has also been used as a screening and confirmatory test for primary aldosteronism in patients with low renin hypertension [74]. Repeated measurements of urinary aldosterone excretion of individuals on a high sodium diet show marked intraindividual variability with differences between 1–88 % (median of 31 %) when two measurements were done 2 weeks apart [75]. This is a probable reason why urinary aldosterone excretion appeared to be less reliable in the diagnosis of primary aldosteronism, especially in normokalemic patients [70]. The basis for the current criteria of > 12 μg/24 h urinary aldosterone excretion while consuming a high salt diet for the diagnosis of primary aldosteronism [74, 76] is arbitrary and not well documented.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

Others have used 14 µg/24 h [77]; early studies used 20 µg/24 h [78]. Moreover, around 14 % of normotensive individuals have values above this number, which might have prognostic significance or might simply represent the high end of the normal conversion rate of aldosterone to aldosterone-18-oxo-glucuronide and, therefore, might not be representative of the production rate of aldosterone [74].

The glucuronidation of mineralocorticoids and glucocorticoids is exerted by several of the UDP-glucuronosyltransferases [79–81]. H293 cells transfected with different human [79] and monkey [80, 81] UDP-glucuronosyltransferase cDNAs demonstrated that of the 18 catalytically active human UD-glucuronosyltransferases found in the liver and kidney, only UGT1A10 and UGT2B7 were capable of converting aldosterone to the 18-oxo-glucuronide; only the UGT2B7 is expressed in the kidney where the bulk of aldosterone is conjugated with the glucuronide [79]. These enzymes also glucuronidate the tetrahydroaldosterones, mainly in the liver. Nonsteroidal anti-inflammatory drugs are glucuronidated by the same enzymes, thus, are competitive antagonists of aldosterone glucuronidation, potentially increasing the concentration and action of aldosterone within the kidney, as well as decreasing the proportion of aldosterone excreted as the 18-oxo-glucuronide [79, 82]. In humans, immunohistochemistry using an antibody against the UGT2B7 demonstrated enzyme expression throughout the proximal, distal convoluted tubules, the loop of Henle, and the collecting ducts [83]. In monkeys, it appears to be primarily in the proximal duct [81]. A further source of variation for the conjugation of aldosterone to glucuronic acid in the human is the existence of two allelic variants of the UGT2B7 [81]. The UGT2B7H$^{(268)}$ possesses 11-fold higher aldosterone glucuronidation efficiency than the UGT2B7Y$^{(268)}$. The multiple drug-resistant *MDR1* gene product P-glycoprotein belongs to the family of ATP-binding cassette transporters that function as transmembrane efflux pumps to translocate substrates from the intracellular to the extracellular space. Aldosterone is transported by P-glycoprotein in the adrenal glomerulosa cell and participates in the efflux of aldosterone from the cells of the zona glomerulosa [84] and other cells, including the kidney where P-glycoprotein is located in the luminal membrane of collecting duct cells [85]. Polymorphisms of the P-glycoprotein do not appear to have a major effect under basal conditions; however, their inhibition by P-glycoprotein inhibitor drugs affects the urinary excretion of aldosterone differently depending on the polymorphism [86].

Tetrahydroaldosterone

The main metabolite of aldosterone is the 3α,5β-tetrahydroaldosterone glucuronide. It is primarily a liver metabolite, corresponding to around half of the aldosterone metabolites [67, 87]. Measuring tetrahydroaldosterone in the urine involves hydrolysis of the glucuronide conjugate with a beta-glucuronidase and measurement by several methods, including radioimmunoassay, high-performance liquid chromatography (HPLC)-MS-MS [88–93]. Since most aldosterone is metabolized to 3α,5β-tetrahydroaldosterone, it has been proposed that it is a better indicator of aldosterone secretion; however, the metabolism of aldosterone to the 3α,5β-tetrahydroaldosterone is affected by different disease states; in particular, it is decreased in congestive heart failure and cirrhosis of the liver [94, 95]. Antihypertensive drug therapy and sodium diet can also affect the proportion of aldosterone metabolized to the 3α,5β-tetrahydroaldosterone; thiazide diuretics decrease and converting enzyme inhibitors increase the proportion of aldosterone metabolized to 3α,5β-tetrahydroaldosterone [87]. Patients with low renin hypertension also preferentially metabolize aldosterone to 3α,5β-tetrahydroaldosterone [96]. A radioimmunoassay was designed using an antibody against 3α,5β-tetrahydroaldosterone-glucuronide isolated from the urine, allowing its direct measurement in urine [97, 98]. This simplified the assay, but unfortunately, the antibody and standards are no longer available. Although there is a good correlation between aldosterone-18-oxo-glucuronide and 3α,5β-tetrahydroaldosterone-glucuronide excretion in normal and hypertensive individuals, there are significant differences in the excretion of these metabolites and urinary 3α,5β-tetrahydroaldosterone appears to be the most reliable in the diagnosis of primary aldosteronism [88, 90].

Urinary free aldosterone

Urinary free aldosterone represents a very small proportion, about 1 %, of the total aldosterone secretion [88]. Measurement of free aldosterone excretion was reported to be equally as good as that of aldosterone-18-oxo-glucuronide for the diagnosis of primary aldosteronism [99]; however, others have reported that urinary free aldosterone is frequently normal in patients with primary aldosteronism, while the excretion of 3α,5β-tetrahydroaldosterone and aldosterone-18-oxo-glucuronide are consistently elevated [88]. As it does not have advantages over the measurements of 3α,5β-tetrahydroaldosterone and aldosterone-18-oxo-glucuronide, urinary free aldosterone is seldom used for diagnostic purposes. Interestingly, a recent publication with a CYP11B2 inhibitor, baxdrostat, used urinary free aldosterone measurements to document the in vivo inhibition of the enzyme [100].

Conclusion

Aldosterone is metabolized primarily in the liver to form several 5α and 5β dihydroaldosterone and tetrahydroaldosterone metabolites, the most abundant of which is 3α,5β-tetrahydroaldosterone, which is glucuronidated for excretion in the kidney. A smaller proportion of aldosterone is glucuronidated in the kidney at carbon 18 to form aldosterone-18-oxo-glucuronide, commonly called urinary aldosterone. Aldosterone metabolism is affected by drugs that alter metabolism and glucuronidation. Urinary excretion of aldosterone-18-oxo-glucuronide is one of the most frequently used measured metabolites for the confirmation of the diagnosis of primary aldosteronism. Although not frequently used, urinary 3α,5β-tetrahydroaldosterone is probably the most reliable metabolite for the estimation of aldosterone secretion in primary aldosteronism.

Acknowledgments

Dr. CEGS is supported by the National Heart, Lung, and Blood Institute grant R01 HL144847, National Institutes of General Medical Sciences U54 GM115428, and Department of Veteran Affairs BX00468.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

 | © 2023. Thieme. All rights reserved.

Funding Information

National Heart, Lung, and Blood Institute — http://dx.doi.org/10.13039/100000050; HL144847; National Institutes of General Medical Sciences — U54 GM115428; USA Department of Veterans' Affairs — BX00468

Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] Miller WL, White PC. History of adrenal research: From ancient anatomy to contemporary molecular biology. Endocr Rev 2023; 44: 70–116

[2] Addison T. Chronics suprarenal insufficiency, usually due to tuberculosis of suprarenal capsule. Lond Med. Gazette 1849; 43: 517–518

[3] Yamashima T. Jokichi Takamine (1854-1922), the samurai chemist, and his work on adrenalin. J Med Biogr 2003; 11: 95–102

[4] Swingle WW, Pfiffner JJ. The revival of comatose adrenalectomized cats with an extract of the suprarenal cortex. Science 1930; 72: 75–76

[5] Hartman FA, Brownell KA. The hormone of the adrenal cortex. Science 1930; 72: 76

[6] Reichstein T, Reich H. The chemistry of the steroids. Annu Rev Biochem 1946; 15: 155–192

[7] Von Euw J, Reichstein T. About components of the adrenal cortex and related substances; Configuration of the cortico steroids. Helv Chim Acta 1947; 30: 205–217

[8] Steiger M, Reichstein T. Desoxy-corticosterone (21-oxy-progesterone). Aus d-3-oxo-etiocholensäure. Helv Chim Acta 1937; 20: 1164

[9] Thorn GW, Howard RP, Emerson K. Treatment of Addison's disease with desoxy-corticosterone acetate, a synthetic adrenal cortical hormone (preliminary report). J Clin Invest 1939; 18: 449–467

[10] Wintersteiner O, Pfiffner JJ. Chemical studies on the adrenal cortex III. Isolation of two new physiologically inactive compounds. J Biol Chem 1936; 127: 291–305

[11] Conn JW, Louis LH, Fajans SS. The probability that compound F (17-hydroxycorticosterone) is the hormone produced by the normal human adrenal cortex. Science 1951; 113: 713–714

[12] Fourman P, Bartter FC, Albright F et al. Effects of 17-hydroxycorticosterone ("compound F") in man. J Clin Invest 1950; 29: 1462–1473

[13] Amelung D, Hubener HJ, Roka L et al. Conversion of cortisone to compound F. J Clin Endocrinol Metab 1953; 13: 1125–1126

[14] Tait SA, Tait JF, Coghlan JP. The discovery, isolation and identification of aldosterone: Reflections on emerging regulation and function. Mol Cell Endocrinol 2004; 217: 1–21

[15] Dorfman RI, Potts AM, Feil ML. Studies on the bioassay of hormones; the use of radiosodium for the detection of small quantities of desoxycorticosterone. Endocrinology 1947; 41: 464–469

[16] Simpson SA, Tait JF. A quantitative method for the bioassay of the effect of adrenal cortical steroids on mineral metabolism. Endocrinology 1952; 50: 150–161

[17] Axelrad BJ, Cates JE, Johnson BB et al. Bioassay of mineralocorticoids: Relationship of structure to physiological activity. Endocrinology 1954; 55: 568–574

[18] Simpson SA, Tait JF, Bush IE. Secretion of a salt-retaining hormone by the mammalian adrenal cortex. Lancet 1952; 1: 226–232

[19] Grundy HM, Simpson SA, Tait JF. Isolation of a highly active mineralocorticoid from beef adrenal extract. Nature 1952; 169: 795–796

[20] Bush IE. Methods of paper chromatography of steroids applicable to the study of steroids in mammalian blood and tissues. Biochem J 1952; 50: 370–378

[21] Tait JF, Tait SAS. A steroid memoir: A decade (or more) of electrocortin (aldosterone). Steroids 1988; 51: 213–250

[22] Deming QB, Luetscher JA. Bioassay of desoxycorticosterone-like material in urine. P Soc Exp Biol Med 1950; 73: 171–175

[23] Luetscher JA Jr., Dowdy A, Harvey J et al. Isolation of crystalline aldosterone from the urine of a child with the nephrotic syndrome. J Biol Chem 1955; 217: 505–512

[24] Deming QB, Luetscher JA Jr. Increased sodium-retaining corticoid excretion in edema, with some observations on the effects of cortisone in nephrosis. J Clin Invest 1950; 29: 808

[25] Luetscher JA Jr., Axelrad BJ. Increased aldosterone output during sodium deprivation in normal men. Proc Soc Exp Biol Med 1954; 87: 650–653

[26] Simpson SA, Tait JF, Wettstein A et al. Isolierung eines neuen kristallisierten hormons aus nebennieren mit besonders hoher wirksamkeit auf den mineralostoffwechsel. Experientia 1953; 9: 333–333

[27] Simpson SA, Tait JF, Wettstein A et al. Konstitution des aldosterons, des neuen mineralocorticoids. Experientia 1953; 10: 132–133

[28] Tait SA, Tait JF. The correspondence of S.A.S. Simpson and J.F. Tait with T. Reichstein during their collaborative work on the isolation and elucidation of the structure of electrocortin (later aldosterone). Steroids 1998; 63: 440–453

[29] Singh N, Taibon J, Pongratz S et al. Absolute content determination by quantitative NMR (qNMR) spectroscopy: A curious case of aldosterone. RSC Adv 2021; 11: 23627–23630

[30] Duax WL, Hauptman H. The crystal structure and molecular conformation of aldosterone. J Am Chem Soc 1972; 94: 54675471

[31] Genard P, Palem-Vliers M, Denoel J et al. Molecular configuration and conformation of aldosterone, 18-hydroxy-11-deoxycorticosterone and a new urinary 18-hydroxy-steroid--an N.M.R. study. J Steroid Biochem 1975; 6: 201–210

[32] Schmidlin J, Anner G, Billeter JR et al. Synthesis in aldosterone-series. I. Total synthesis of racemic aldosterone. Experientia 1955; 11: 365–368

[33] Barton DHR, Basu NK, Day MJ et al. Improved synthesis of aldosterone. J Chem Soc 1975; Perkins Trans I 2243–2251

[34] Barton DHR, Beaton JM. A synthesis of aldosterone acetate. J Am Chem Soc 1961; 83: 4083–4089

[35] Giroud CJP, Stachenko J, Venning EH. Secretion of aldosterone by the zona glomerulosa of rat adrenal glands incubated in vitro. Proc Soc Exp Biol Med 1956; 92: 154–158

[36] Spat A, Hunyady L. Control of aldosterone secretion: A model for convergence in cellular signaling pathways. Physiol Rev 2004; 84: 489–539

[37] Hattangady NG, Olala LO, Bollag WB et al. Acute and chronic regulation of aldosterone production. Mol Cell Endocrinol 2012; 350: 151–162

[38] Ayres PJ, Pearlman WH, Tait JF et al. The biosynthetic preparation of [16-3H]aldosterone and [16-3H] corticosterone. Biochem J 1958; 70: 230–236

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

[39] Tait JF. Review: The use of isotopic steroids for the measurement of production rates in vivo. J Clin Endocrinol Metab 1963; 23: 1285–1297

[40] Ulick S, Laragh JH, Lieberman S. The isolation of urinary metabolite of aldosterone and its use to measure the rate of secretion of aldosterone by the adrenal cortex of man. Trans Ass Am. Phy 1958; 71: 225–235

[41] Flood C, Layne DS, Ramcharan S et al. An investigation of the urinary metabolites and secretion rates of aldosterone and cortisol in man and a description of methods for their measurement. Acta Endocrinol (Copenh) 1961; 36: 237–264

[42] Tait JF, Tait SA, Little B et al. The disappearance of 7-H-3-d-aldosterone in the plasma of normal subjects. J Clin Invest 1961; 40: 72–80

[43] Tait JF, Bougas J, Little B et al. Splanchnic extraction and clearance of aldosterone in subjetes with minimal and marked cardiac dysfunction. J Clin Endocrinol Metab 1965; 25: 219–228

[44] Ulick S, Lieberman S. Evidence for the occurence of a metabolite of aldosterone in urine. J Am Chem Soc 1957; 79: 6567–6568

[45] Ulick S, Laragh JH, Lieberman S. The isolation of a urinary metabolite of aldosterone and its use to measure the rate of secretion of aldosterone by the adrenal cortex of man. Trans Assoc Am Physicians 1958; 71: 225–235

[46] Ulick S, Ramirez LC. Isolation and synthesis of the major metabolites of aldosterone and 18-hydroxycorticosterone. Meth Enzy 1975; 36: 503–512

[47] Kelly WG, Bandi L, Lieberman S. Isolation and characterization of human urinary metabolites of aldosterone. V. Dihydroaldosterone and 21-deoxytetrahydroaldosterone. Biochemistry 1963; 2: 1249–1254

[48] Kelly WG, Bandi L, Lieberman S. Isolation and characterization of human urinary metabolites of aldosterone. Iv. The synthesis and stereochemistry of two bicyclic acetal metabolites. Biochemistry 1963; 2: 1243–1249

[49] Kelly WG, Bandi L, Shoolery JN et al. Isolation and characterization of aldosterone metabolites from human urine; two metabolites bearing a bicyclic acetal structure. Biochemistry 1962; 1: 172–181

[50] Lewicka S, Vecsei P, Bige K et al. Urinary excretion of aldosterone metabolite Kelly-M1 in patients with adrenal dysfunction. J Steroid Biochem 1988; 29: 333–339

[51] Winter J, Shackleton CH, O'Rourke S et al. Bacterial formation of aldosterone metabolites. J Steroid Biochem 1984; 21: 563–569

[52] Cozza EN, Lantos CP, Burton G. A highly lipophilic form of aldosterone. Isolation and characterization of an aldosterone dimer. J Steroid Biochem 1985; 23: 511–516

[53] Harnik M, Kashman Y, Cojocaru M et al. 18,21-Anhydroaldosterone and derivatives. Steroids 1989; 54: 11–19

[54] Latif SA, Morris DJ, Wei L et al. 18-substituted steroids--Part 17. 2 Alpha-hydroxylated liver metabolites of aldosterone identified by high-field [1H]NMR spectroscopy. J Steroid Biochem 1989; 33: 1119–1125

[55] Kirk DN, Burke PJ, Toms HC et al. 18-Substituted steroids. Part 15. 6 Beta-hydroxylation of aldosterone by liver. Steroids 1989; 54: 169–184

[56] Morris DJ. The metabolism and mechanism of action of aldosterone. Endocr Rev 1981; 2: 234–247

[57] Kenyon CJ, Brem AS, McDermott MJ et al. Antinatriuretic and kaliuretic activities of the reduced derivatives of aldosterone. Endocrinology 1983; 112: 1852–1856

[58] Gomez-Sanchez CE, Smith JS, Ferris MW et al. Renal receptor binding activity of reduced metabolites of aldosterone: Evidence for a mineralocorticoid effect outside of the classic aldosterone receptor system. Endocrinology 1984; 115: 712–715

[59] Gorsline J, Latif SA, Morris DJ. Changes in 5 alpha- and 5 beta-reductase pathways of aldosterone metabolism by dietary sodium. Am J Hypertens 1988; 1: 272–275

[60] Morris DJ, Kenyon CJ, Latif SA et al. The possible biological role of aldosterone metabolites. Hypertension 1983; 5: I35–I40

[61] Grose JH, Nowaczynski W, Kuchel O et al. Isolation of aldosterone urinary metabolites, glucuronides and sulfate. J Steroid Biochem 1973; 4: 551–566

[62] Jowett TP, Slater JD. Aldosterone 21-sulphate in man. J Steroid Biochem 1983; 18: 471–479

[63] Luetscher JA Jr., Axelrad BJ. Sodium-retaining corticoid in the urine of normal children and adults and of patients with hypoadrenalism or hypopituitarism. J Clin Endocrinol Metab 1954; 14: 1086–1089

[64] Axelrad BJ, Cates JE, Johnson BB et al. Aldosterone in urine of normal man and of patients with oedema; its increased recovery after hydrolysis with acid and with beta-glucuronidase. Br Med J 1955; 1: 196–199

[65] Pasqualini JR, Uhrich F, Jayle MF. Contribution to the study of the structure of the aldosterone-conjugate isolated from human urine. Biochim Biophys Acta 1965; 104: 515–523

[66] Underwood RH, Tait JF. Purification, partial characterization and metabolism of an acid labile conjugate of aldosterone. J Clin Endocrinol Metab 1964; 24: 1110–1124

[67] Luetscher JA, Camargo CA, Cohn AP et al Observations on metabolism of aldosterone in man. Ann Intern Med 1963; 59: 1–7

[68] Underwood RH, Flood CA, Tait SA et al. A comparison of methods for the acid hydrolysis of a urinary conjugate of aldosterone. J Clin Endocrinol Metab 1961; 21: 1092–1098

[69] Yin Y, Yu S, Qiu L et al. Establishment of a rapid and simple liquid chromatography tandem mass spectrometry method for measuring aldosterone in urine. J Chromatogr B Analyt Technol Biomed Life Sci 2019; 1113: 84–90

[70] Schirpenbach C, Seiler L, Maser-Gluth C et al. Confirmatory testing in normokalaemic primary aldosteronism: The value of the saline infusion test and urinary aldosterone metabolites. Eur J Endocrinol 2006; 154: 865–873

[71] Vecsei P, Abdelhamid S, Mittelstadt GV et al. Aldosterone metabolites and possible aldosterone precursors in hypertension. J Steroid Biochem 1983; 19: 345–351

[72] Tait JF, Little B. The metabolism of orally and intravenously administered labeled aldosterone in pregnant subjects. J Clin Invest 1969; 47: 2423–2429

[73] Funder JW, Carey RM, Mantero F et al. The management of primary aldosteronism: Case detection, diagnosis, and treatment: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2016; 101: 1889–1916

[74] Brown JM, Siddiqui M, Calhoun DA et al. The unrecognized prevalence of primary aldosteronism: A cross-sectional study. Ann Intern Med 2020; 173: 10–20

[75] Ceral J, Malirova E, Ballon M et al. The role of urinary aldosterone for the diagnosis of primary aldosteronism. Horm Metab Res 2014; 46: 663–667

[76] Young WF. Primary aldosteronism: Renaissance of a syndrome. Clin Endocrinol (Oxf) 2007; 66: 607–618

[77] Bravo EL. Primary aldosteronism: New approaches to diagnosis and management. Cleve Clin J Med 1993; 60: 379–386

[78] Conn JW, Knopf RF, Nesbit RM. Clinical characteristics of primary aldosteronism from an analysis of 145 cases. Am J Surg 1964; 107: 159–172

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

[79] Knights KM, Winner LK, Elliot DJ et al. Aldosterone glucuronidation by human liver and kidney microsomes and recombinant UDP-glucuronosyltransferases: Inhibition by NSAIDs. Br J Clin Pharmacol 2009; 68: 402–412

[80] Girard C, Barbier O, Turgeon D et al. Isolation and characterization of the monkey UGT2B30 gene that encodes a uridine diphosphate-glucuronosyltransferase enzyme active on mineralocorticoid, glucocorticoid, androgen and oestrogen hormones. Biochem J 2002; 365: 213–222

[81] Girard C, Barbier O, Veilleux G et al. Human uridine diphosphate-glucuronosyltransferase UGT2B7 conjugates mineralocorticoid and glucocorticoid metabolites. Endocrinology 2003; 144: 2659–2668

[82] Knights KM, Mangoni AA, Miners JO. Non-selective nonsteroidal anti-inflammatory drugs and cardiovascular events: Is aldosterone the silent partner in crime? Br J Clin Pharmacol 2006; 61: 738–740

[83] Gaganis P, Miners JO, Brennan JS et al Human renal cortical and medullary UDP-glucuronosyltransferases (UGTs): Immunohistochemical localization of UGT2B7 and UGT1A enzymes and kinetic characterization of S-naproxen glucuronidation. J Pharmacol Exp Ther 2007; 323: 422–430

[84] Bello-Reuss E, Ernest S, Holland OB et al. Role of multidrug resistance P-glycoprotein in the secretion of aldosterone by human adrenal NCI-H295 cells. Am J Physiol - Cell Physiol 2000; 278: 1256–1265

[85] Zolk O, Jacobi J, Pahl A et al. MDR1 genotype-dependent regulation of the aldosterone system in humans. Pharmacogenet Genomics 2007; 17: 137–144

[86] Marques P, Courand PY, Gouin-Thibault I et al. P-glycoprotein influences urinary excretion of aldosterone in healthy individuals. J Hypertens 2019; 37: 2225–2231

[87] Griffing GT, Wilson TE, Melby JC. Altered fractional tetrahydroaldosterone excretion during pharmacological blockade and activation of the renin-aldosterone system. J Clin Endocrinol Metab 1982; 55: 1217–1221

[88] Abdelhamid S, Blomer R, Hommel G et al. Urinary tetrahydroaldosterone as a screening method for primary aldosteronism: A comparative study. Am J Hypertens 2003; 16: 522–530

[89] Abdelhamid S, Vecsei P, Haack D et al. Dissociation in the excretion of different aldosterone metabolites and unmetabolized ('free') aldosterone in hypertension. Clin Sci (Lond) 1979; 57: 409–414

[90] Gomez-Sanchez CE, Holland OB. Urinary tetrahydroaldosterone and aldosterone-18-glucuronide excretion in white and black normal subjects and hypertensive patients. J Clin Endocrinol Metab 1981; 52: 214–219

[91] Holland OB, Risk M, Brown H et al. High-performance liquid chromatography in the radioimmunoassay of urinary tetrahydroaldosterone. J Chromatogr 1987; 385: 393–396

[92] Ishida J, Sonezaki S, Yamaguchi M et al. High-performance liquid chromatographic determination of 3 alpha,5 beta-tetrahydroaldosterone in human urine with chemiluminescence detection. Analyst 1992; 117: 1719–1724

[93] Pratt JH, Holbrook MM, Dale SL et al. The measurement of urinary tetrahydroaldosterone by radioimmunoassay. J Steroid Biochem 1977; 8: 677–681

[94] Camargo CA, Dowdy AJ, Hancock EW et al. Decreased plasma clearance and hepatic extraction of aldosterone in patients with heart failure. J Clin Invest 1965; 44: 356–365

[95] Cheville RA, Luetscher JA, Hancock EW et al. Distribution, conjugation, and excretion of labeled aldosterone in congestive heart failure and in controls with normal circulation: Development and testing of a model with an analog computer. J Clin Invest 1966; 45: 1302–1316

[96] Griffing GT, Wilson TE, Melby JC. Alterations in aldosterone secretion and metabolism in low renin hypertension. J Clin Endocrinol Metab 1990; 71: 1454–1460

[97] Alvarez MN, Carpenter PC, Mattox VR. Isolation of tetrahydroaldosterone 3beta-glucosiduronic acid from urine. J Steroid Biochem 1976; 7: 661–664

[98] Mattox VR, Nelson AN. Determination of urinary tetrahydroaldosterone glucosiduronic acid by radioimmunoassay. J Steroid Biochem 1981; 14: 243–249

[99] Deck KA, Champion PK Jr., Conn JW. Urinary free aldosterone in healthy people and in patients with primary aldosteronism. J Clin Endocrinol Metab 1973; 36: 756–760

[100] Freeman MW, Halvorsen YD, Marshall W et al. Phase 2 trial of baxdrostat for treatment-resistant hypertension. N Engl J Med 2023; 388: 395–405. DOI:10.1056/NEJMoa2213169

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.