Pathophysiology of Primary Aldosteronism

Subjects: Medicine, General & Internal

Contributor: Natalia Ekman, Ashley B. Grossman, Dorota Dworakowska

Primary aldosteronism (PA), a significant and curable cause of secondary hypertension, is seen in 5–10% of hypertensive patients, with its prevalence contingent upon the severity of the hypertension. The principal aetiologies of PA include bilateral idiopathic hypertrophy (BIH) and aldosterone-producing adenomas (APAs), while the less frequent causes include unilateral hyperplasia, familial hyperaldosteronism (FH) types I-IV, aldosterone-producing carcinoma, and ectopic aldosterone synthesis. This condition, characterised by excessive aldosterone secretion, leads to augmented sodium and water reabsorption alongside potassium loss, culminating in distinct clinical hallmarks: elevated aldosterone levels, suppressed renin levels, and hypertension. Notably, hypokalaemia is present in only 28% of patients with PA and is not a primary indicator. The association of PA with an escalated cardiovascular risk profile, independent of blood pressure levels, is notable. Patients with PA exhibit a heightened incidence of cardiovascular events compared to counterparts with essential hypertension, matched for age, sex, and blood pressure levels.

Keywords: primary aldosteronism (PA) ; hypertension ; cardiovascular risk in primary aldosteronism ; adrenal vein sampling (AVS)

1. Introduction

PA is the most common and curable cause of secondary hypertension [1]. PA was initially described by Lityński in Poland in 1953, then 2 years later in 1955 by Conn in the USA [2]. PA is associated with excessive and autonomous production of aldosterone. The three hallmark signs of PA are a high aldosterone blood level, a suppressed renin level, and hypertension [3]. Hypokalaemia had originally been considered a principal feature of PA; however, recent studies have reported that hypokalaemia is present only in 28% of PA patients. The most common causes of PA are bilateral idiopathic hypertrophy (BIH) (60% of cases) and aldosterone-producing adenomas (APAs; called Conn's Syndrome) (35% of cases, although these percentages are changing over time) [2]. The rare causes of PA are unilateral hyperplasia, familial hyperaldosteronism (types I–IV), aldosterone-producing carcinoma, and ectopic aldosterone production [1]. PA was formerly thought to be a rare cause of mild-to-moderate hypertension (<1%) and hypokalaemia was one of the main conditions for diagnosis [4][5], but recent work has indicated that PA may be considered to be the most common cause of secondary hypertension [1]. PA is now considered to be a factor in 5–10% of all patients with hypertension [4][5][6]. Such studies have reported that the prevalence of PA depends on the severity of hypertension; the higher the degree of hypertension, the higher the prevalence of PA [7].

2. Physiology

Aldosterone is a steroid hormone produced in the adrenal zona glomerulosa. The main factors inducing the production of aldosterone are Angiotensin II and a high blood potassium level [4]. Other contributing factors, although to a lesser extent, include adrenocorticotropic hormone (ACTH), antidiuretic hormone (ADH), and β-endorphin. Aldosterone affects epithelial cells (the distal tube and collecting duct of the kidney, colonic mucosa, and sweat glands) through interaction with the mineralocorticoid receptor (MR). MRs are located in the cytoplasm of these cells. Aldosterone is lipophilic and easily diffuses through the cell membrane. Once there, aldosterone binds to MR, then the MR dimerises and translocates into the nucleus [1].

In the nucleus, dimerised MRs bind to a specific DNA-binding site and induce the process of gene transcription, leading to specific peptide products. In addition to its genomic function, aldosterone influences MR in a rapid non-genomic manner [5][8]. Aldosterone's action on the distal tubes or collecting ducts of the kidney activates the production of the amiloride-sensitive epithelial sodium channel on the luminal side. Sodium is reabsorbed by this channel; the reabsorption of sodium impacts the hyperosmolar environment, causing the parallel reabsorption of water from urine to blood. This results in increased volume load [9]. Moreover, this process is accompanied by potassium excretion to obtain a balanced electrochemical gradient. Furthermore, aldosterone causes the urinary excretion of H+, causing metabolic alkalosis.

Moreover, MR is also expressed in endothelial cells, vascular smooth muscle cells, cardiomyocytes, and some neurons [1]. Studies suggest that aldosterone binding to these receptors might cause oxidative stress, endothelial dysfunction, inflammation, and fibrosis in the walls of vessels or the heart [10]. Thus, hypertension of PA might be partly caused by sodium and water reabsorption and vasoconstriction of the arteries and may have direct cardiac effects [10].

3. Pathophysiology of Primary Aldosteronism

Primary aldosteronism is mainly caused by adrenal gland adenomas or bilateral idiopathic hypertrophy of the adrenal glands. In addition to these causes, there are also rare conditions related to PA including unilateral hypertrophy, familial hyperaldosteronism (types I–IV), aldosterone-producing carcinoma, and ectopic aldosterone production [11]. For many years, the precise pathogenetic mechanisms of these disorders were only poorly understood. Traditional aspects of PA diagnosis are mainly related to the differentiation between unilateral or bilateral forms of the disease, relevant to the appropriate therapy.

In recent years, researchers have discovered many genetic abnormalities underlying sporadic and familial forms of PA and, as such, useful markers for improving diagnosis and treatment in the future.

Recent advances in understanding PA, especially concerning APAs, highlight the significant role of somatic mutations. Currently, the molecular characteristics of APAs are widely studied due to the development of molecular techniques and include such accurate analytic methods as exome sequencing, transcriptome sequencing, and the assessment of epigenetic changes such as DNA methylations in selected mutations [12]. Approximately 90% of APAs present somatic mutations that lead to aldosterone overproduction. These mutations are predominantly found in genes such as *KCNJ5, ATP2B3, ATP1A1, CACNA1D,* and *CACNA1H* [13].

The *CACNA1D* gene encodes a specific protein for a subunit of the L-type calcium channel Ca_V1.3. The main function of this channel is the transport of calcium ions into cells in response to depolarization. Mutation of the *CACNA1D* gene causes increased permeability to calcium ions, which finally induces aldosterone overproduction and cell proliferation in the adrenal zona glomerulosa. In addition, APAs with *CACNA1D* mutations are composed of zona glomerulosa-like cells and are smaller than APAs with *KCNJ5* mutations [14].

Other mutations that occur in APAs are *ATP1A1* and *ATP2A3*. *ATP1A1* and *ATP2B3* are genes that encode different types of ATPase enzymes; the *ATP1A1* gene encodes a subunit of Na+/K+ ATPase while *ATP2B3* encodes a plasma membrane Ca2+ ATPase. Mutations of these genes in APAs cause abnormal permeability to Na+ or H+ and increase aldosterone production. These mutations have not been observed in familial hyperaldosteronism [15].

One of the most common mutations reported in APAs is of *KCNJ5*, which encodes a potassium channel. Mutation of this gene causes increased sodium influx and subsequent depolarization, which leads to increased calcium levels in cells and finally stimulates aldosterone production. In addition, the presence of *KCNJ5* mutations in APAs is associated with certain clinical features such as more severe forms of hypertension, and more often occurs in female and younger patients [15]. In addition, the Japan Primary Aldosteronism Study (JPAS) conducted research on the molecular characteristics of *KCNJ5*-mutated APAs. This study demonstrated that APAs with somatic *KCNJ5* mutation have global DNA hypomethylation and transcriptomic profiles accompanied by changes in specific genes such as Wnt signalling, cytokine, and inflammatory response pathways. Thus, *KCNJ5*-mutated APAs constitute a specific subgroup of APAs [12]. Moreover, several studies investigating steroid profiling in PA diagnostics demonstrate that hybrid steroids 18-hydroxycortisol (*18OHF*) and 18-oxocortisol (*18oxoF*) are characteristic of APAs with *KCNJ5* mutations [16].

Somatic mutations present in the majority of APAs are generally responsible for the autonomous overproduction of aldosterone. Often the same mutations are discovered in patients with BIH and familial hyperaldosteronism (FH). There are several types of FH, each associated with different genetic mutations (germline mutations).

FH type I is characterized by severe hypertension in childhood with autosomal dominant inheritance. FH type I, also known as glucocorticoid-remediable aldosteronism, is caused by a unique genetic mutation involving the *CYP11B1* and *CYP11B2* genes. This mutation results in a chimeric gene combining elements of both genes; an unequal cross-over occurs between the *CYP11B1* gene, which encodes steroid 11β-hydroxylase, and the *CYP11B2* gene, responsible for aldosterone synthase. This chimeric gene produces aldosterone synthase, which is abnormally activated by ACTH instead of angiotensin II. These changes lead to the overproduction of aldosterone in patients with FH type I. However, this unique mutation also offers the possibility to control aldosterone production with glucocorticoids [17].

FH type II is associated with mutations in the *ClCN2* gene, which encodes the chloride channel ClC2. These changes cause the activation of calcium signalling and increased CYP11B2 expression on the membranes of zona glomerulosa cells. Diagnosis is based on clinical criteria and family history [18].

In FH type III, there are germline mutations in *KCNJ5*. This type of FH is often associated with severe hypertension. In addition, patients with FH type III can develop APAs and adrenal gland hyperplasia [19].

FH type IV is associated with mutations in *CACNA1H*, which encodes subunit calcium channels and activates calcium signalling. In each case, the result of these changes is inappropriate aldosterone biosynthesis [19].

In summary, most of the mutations discovered in PA patients are located in genes encoding ion channels and pumps. These mutations lead to increased calcium concentrations in the zona glomerulosa cells, which influences the expression of *CYP11B2* and, finally, the overproduction of aldosterone. Such new knowledge about genetic mutations related to the pathogenesis of PA could lead to the development of new pharmacological treatment targeting mutated proteins [20], whereas understanding the mutations that occur in FH could improve the diagnosis of positive patients in the early stages of the disease, before the onset of symptoms or cardiovascular complications [21]. In addition, the molecular characterisation of APAs using more advanced techniques, such as the analysis and integration of transcriptome and methylome, could provide new possibilities in the diagnosis and treatment of PA.

References

1. Brian Byrd, J.; Turcu, A.F.; Auchus, R.J. Primary Aldosteronism: Practical Approach to Diagnosis and Management. Circulation 2018, 138, 823–835.
2. Farrugia, F.-A.; Zavras, N.; Martikos, G.; Tzanetis, P.; Charalampopoulos, A.; Misiakos, E.P.; Sotiropoulos, D.; Koliakos, N. A Short Review of Primary Aldosteronism in a Question and Answer Fashion. Endocr. Regul. 2018, 52, 27–40.
3. Young, W.F. Diagnosis and Treatment of Primary Aldosteronism: Practical Clinical Perspectives. J. Intern. Med. 2018, 285, 126–148.
4. Funder, J.W.; Carey, R.M.; Mantero, F.; Murad, M.H.; Reincke, M.; Shibata, H.; Stowasser, M.; Young, W.F. The Management of Primary Aldosteronism: Case Detection, Diagnosis, and Treatment: An Endocrine Society Clinical Practice Guideline. J. Clin. Endocrinol. Metab. 2016, 101, 1889–1916.
5. Funder, J.W. Aldosterone and Mineralocorticoid Receptors in the Cardiovascular System. Prog. Cardiovasc. Dis. 2010, 52, 393–400.
6. Funder, J.W.; Carey, R.M. Primary Aldosteronism: Where Are We Now? Where to From Here? Hypertension 2022, 79, 726–735.
7. Rossi, G.P.; Bernini, G.; Caliumi, C.; Desideri, G.; Fabris, B.; Ferri, C.; Ganzaroli, C.; Giacchetti, G.; Letizia, C.; Maccario, M.; et al. A Prospective Study of the Prevalence of Primary Aldosteronism in 1,125 Hypertensive Patients. J. Am. Coll. Cardiol. 2006, 48, 2293–2300.
8. Cannavo, A.; Bencivenga, L.; Liccardo, D.; Elia, A.; Marzano, F.; Gambino, G.; D'Amico, M.L.; Perna, C.; Ferrara, N.; Rengo, G.; et al. Aldosterone and Mineralocorticoid Receptor System in Cardiovascular Physiology and Pathophysiology. Oxid. Med. Cell. Longev. 2018, 1204598.
9. Hering, D.; Trzebski, A.; Narkiewicz, K. Recent Advances in the Pathophysiology of Arterial Hypertension: Potential Implications for Clinical Practice. Pol. Arch. Intern. Med. 2017, 127, 195–204.
10. Callera, G.E.; Montezano, A.C.I.; Yogi, A.; Tostes, R.C.; He, Y.; Schiffrin, E.L.; Touyz, R.M. C-Src—Dependent Nongenomic Signaling Responses to Aldosterone Are Increased in Vascular Myocytes from Spontaneously Hypertensive Rats. Hypertension 2005, 46, 1032–1038.
11. Todesco, S.; Mantero, F.; Terribile, V.; Guarnieri, G.F.; Borsatti, A. Ectopic Aldosterone Production. Lancet 1973, 302, 443.
12. Murakami, M.; Yoshimoto, T.; Nakabayashi, K.; Nakano, Y.; Fukaishi, T.; Tsuchiya, K.; Minami, I.; Bouchi, R.; Okamura, K.; Fujii, Y.; et al. Molecular Characteristics of the KCNJ5 Mutated Aldosterone-Producing Adenomas. Endocr.-Relat. Cancer 2017, 24, 531–541.
13. Azizan, E.A.B.; Drake, W.M.; Brown, M.J. Primary Aldosteronism: Molecular Medicine Meets Public Health. Nat. Rev. Nephrol. 2023, 19, 788–806.

14. Scholl, U.I.; Goh, G.; Stölting, G.; de Oliveira, R.C.; Choi, M.; Overton, J.D.; Fonseca, A.L.; Korah, R.; Starker, L.F.; Kunstman, J.W.; et al. Somatic and Germline CACNA1D Calcium Channel Mutations in Aldosterone-Producing Adenomas and Primary Aldosteronism. Nat. Genet. 2013, 45, 1050–1054.
15. Seidel, E.; Schewe, J.; Scholl, U.I. Genetic Causes of Primary Aldosteronism. Exp. Mol. Med. 2019, 51, 1–12.
16. Rege, J.; Turcu, A.F.; Rainey, W.E. Primary Aldosteronism Diagnostics: KCNJ5 Mutations and Hybrid Steroid Synthesis in Aldosterone-Producing Adenomas. Gland Surg. 2020, 9, 3–13.
17. Sanga, V.; Seccia, T.M.; Rossi, G.P. A Systematic Review of Pathophysiology and Management of Familial Hyperaldosteronism Type 1 in Pregnancy. Endocrine 2021, 74, 5–10.
18. Scholl, U.I.; Stölting, G.; Schewe, J.; Thiel, A.; Tan, H.; Nelson-Williams, C.; Vichot, A.A.; Jin, S.C.; Loring, E.; Untiet, V.; et al. CLCN2 Chloride Channel Mutations in Familial Hyperaldosteronism Type II. Nat. Genet. 2018, 50, 349–354.
19. Scholl, U.I.; Stölting, G.; Nelson-Williams, C.; Vichot, A.A.; Choi, M.; Loring, E.; Prasad, M.L.; Goh, G.; Carling, T.; Juhlin, C.C.; et al. Recurrent Gain of Function Mutation in Calcium Channel CACNA1H Causes Early-Onset Hypertension with Primary Aldosteronism. eLife 2015, 4, e06315.
20. Zennaro, M.-C.; Boulkroun, S.; Fernandes-Rosa, F.L. Pathogenesis and Treatment of Primary Aldosteronism. Nat. Rev. Endocrinol. 2020, 16, 578–589.
21. Reincke, M.; Bancos, I.; Mulatero, P.; Scholl, U.I.; Stowasser, M.; Williams, T.A. Diagnosis and Treatment of Primary Aldosteronism. Lancet Diabetes Endocrinol. 2021, 9, 876–892.