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Review

Somatic mutations of the *ATP1A1* gene and aldosterone-producing adenomas

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ABSTRACT

Primary aldosteronism is the most common form of secondary hypertension. It affects approximately 10% of patients with hypertension and causes greater cardiovascular morbidity and mortality compared to essential hypertension of similar severity and duration. The cause of primary aldosteronism in about half of these patients is an aldosterone-producing adenoma; over half of these adenomas have mutations in one of several ion channels and pumps, including the potassium channel KCNJ5, calcium channel $Ca_v1.3$, $\alpha1$ subunit of the sodium potassium ATPase, and membrane calcium ATPase 3. This review concentrates on the molecular and physiological mechanisms by which mutations of the *ATP1A1* gene increase aldosterone production.

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1. Introduction

Primary aldosteronism was first described by Jerome Conn in 1955 (Conn, 1955) in patients presenting with hypertension and hypokalemia. A review of his experience at the University of Michigan demonstrated that approximately 20% of hypertensives had primary aldosteronism due to an aldosterone-producing adenoma (Conn et al., 1964). Subsequent studies suggested that this high incidence of primary aldosteronism was due to a selection bias, as this was a referral clinic and one of the few institutions where aldosterone could be measured. The incidence was found to be as low as 0.1% (Berglund et al., 1976) based on a retrospective review of Swedish patients with hypertension. A major cause of this discrepancy may have been the use of hypokalemia as a major part of the criteria for screening for primary aldosteronism using serum of plasma obtained in the standard methods of using a tourniquet for blood sampling that

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increases potassium in the blood (Abdelhamid et al., 2003). The most potent regulator of aldosterone secretion is the renin–angiotensin system. Renin secreted from the kidney in response to a decrease in blood pressure generates angiotensin II, the most potent stimulator of aldosterone synthesis and secretion by adrenal glomerulosa cells. Aldosterone actions in the kidney, vessels, heart and sympathetic nervous system synergize with those of angiotensin II to increase blood pressure and suppress renin. Hiramatsu et al. (1981) devised a screening test based on this feedback mechanism of the renin–angiotensin–aldosterone system (RAAS): autonomous secretion of aldosterone in PA produces an increase in the aldosterone:plasma renin activity ratio. This aldo:renin ratio, now the standard screening test to select patients for further confirmation studies, has established that PA is the most common form of secondary hypertension, causing about 1% of hypertension in the general population and around 6–10% in the hypertensive population (Fardella et al., 2000; Funder et al., 2008; Hannemann et al., 2012; Mosso et al., 2003). Primary aldosteronism was classified into several groups, the most common due a unilateral benign aldosterone-producing adenoma and idiopathic hyperaldosteronism, or bilateral zona glomerulosa hyperplasia, with aldosterone production coming from both adrenals. Less common forms of PA are unilateral hyperplasia, adrenal carcinoma producing aldosterone, and rare familial cases. For many years research concentrated on the differentiation of aldosterone-producing adenoma from other forms of primary aldosteronism, as the tumors could be treated with surgery resulting in either cure or significant improvement in the hypertension and usually full correction of the hypokalemia. Idiopathic hyperaldosteronism is treated medically. Primary aldosteronism is associated with a significant increase in cardiovascular morbidity and mortality. Atrial fibrillation, congestive heart failure and ischemic heart disease are 2–5 times more prevalent in patients with PA (Savard et al., 2013) and there was an increase in 14 yr. mortality in aldosterone-producing adenoma patients over matched patients with essential hypertension in the German Conn's Registry (Reincke et al., 2012).

2. Aldosterone-producing adenomas

2.1. Molecular pathogenesis of aldosterone-producing adenoma

Studies of pathogenesis of aldosterone-producing adenomas up to 2011 concentrated in the search for altered expression of genes using microarray technology, particularly of aberrant G-protein-coupled receptors that might regulate aldosterone production. Aberrant receptors were found in many aldosterone-producing adenomas including GnRH (Ye et al., 2007), LH (Saner-Amigh et al., 2006), vasopressin (Perraudin et al., 2006), serotonin (Ye et al., 2007), endothelin receptor type B-like (GPR37) and glutamate receptor metabotropic 3 (Ye et al., 2007). These receptors may play a role in occasional patients with PA (Zwermann et al., 2009), but do not explain the pathogenesis of aldosterone-producing adenomas in most patients (Ye et al., 2007). During the 1970–1980s there was a futile search for unidentified aldosterone-stimulating factors to explain the pathogenesis of idiopathic hyperaldosteronism or even aldosterone-producing adenomas .

2.2. Somatic mutation of the KCNJ5 gene

A major advance occurred in 2011 when the Lifton group reported the results of whole exome sequencing of a group of aldosterone-producing adenomas and the identification of somatic mutations of the gene for G-protein-activated potassium inward rectifying channel *KCNJ5*, with mutations G151R and L168R, in approximately 30% of the aldosterone-producing adenomas studied and an additional mutation at T158A a family of patients with familial hyperaldosteronism type 3 (Choi et al., 2011). These mutations occur in or next to the selectivity filter of the channel of KCNJ5, also called the Kir3.4 channel. Since then multiple other mutations of the *KCNJ5* have been found (reviewed in Gomez-Sanchez and Oki, 2014). These mutations within the same region of the selectivity filter and some outside the selectivity filter (Murthy et al., 2014) result in a significant decrease in potassium selectivity and leakage of sodium to the cell, depolarizing the membrane and opening of calcium channels, resulting in activation of the calcium-calmodulin kinase pathway and transcriptional activation of the enzymatic machinery for the biosynthesis of aldosterone (Choi et al., 2011; Oki et al., 2012; Tauber et al., 2014). In European cohorts somatic mutations of the KCNJ5 in aldosterone-producing adenomas have been found preferentially in younger females with a total incidence of around 30–40% of aldosterone-producing adenomas (Akerstrom et al., 2012; Azizan et al., 2012; Boulkroun et al., 2012; Fernandes-Rosa et al., 2014; Kuppusamy et al., 2014; Mulatero et al., 2012; Scholl et al., 2012; Taguchi et al., 2012; Williams et al., 2014), while in Japan the incidence is around 60% with no sexual predominance (Taguchi et al., 2012). Germ line mutations of the *KCNJ5* gene may not be rare. A single nucleotide polymorphism that adversely affected inward-rectification and selectivity of the KCNJ5 channel was found in 5% of a cohort of 251 patients with primary aldosteronism in the United Kingdom and Australia (Murthy et al., 2014). A significant number of these patients had bilateral hyperaldosteronism (Murthy et al., 2014). The adrenal glands with an aldosterone-producing adenoma expressing KCNJ5 mutations often exhibit other abnormalities, including hyperplastic regions surrounding the adenoma and nodules that express stem/progenitor cell markers (Boulkroun et al., 2010; Boulkroun et al., 2011). Not all of these nodules express the KCNJ5 mutations but those that do also express the last enzyme in the steroidogenic cascade for aldosterone biosynthesis, the CYP11B2 enzyme (Dekkers et al., 2014).

Further exome sequencing of aldosterone-producing adenomas uncovered other somatic gene mutations, including those of the *ATP1A1* (sodium/potassium ATPase alpha subunit), *ATP2B3* (membrane calcium ATPase 3 or PMCA3) and *CACNA1D* (calcium channel, $Ca_v1.3$) genes (Azizan et al., 2013; Beuschlein et al., 2013; Scholl et al., 2013). Table 1 shows the relative incidence of the various mutations in the series reported.

Table 1
KCNJ5, ATP1A1, ATP2B3 and CACNA1D mutations prevalence in aldosterone-producing adenoma from different centers.

Mutations	KCNJ5	ATP1A1	ATP2B3	CACNA1D
Beuschlein et al., 2013	–	16/308 (5.2%)	5/308 (1.6%)	–
Azizan et al., 2013	30/73 (41%)	12/152(7.9%)	–	12/152 (7.9%)
Scholl et al., 2013	–	–	–	7/64 (11%)
Williams et al., 2014	44/112 (39.3%)	7/112 (6.3%)	1/112 (0.9%)	–
Dutta et al., 2014	11/35 (31%)	2/35 (6%)	3/35 (9%)	–
Fernandes-Rosa et al., 2014	180/474 (38%)	25/474 (5.3%)	8/474 (1.7%)	44/474 (9.3%)
Kuppusamy et al., 2014	48/195 (24.6%)	3/195 (1.5%)	1/195 (0.5%)	–