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Commentary

Many Channels Lead to Aldosterone☆

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Aldosterone secretion is under the control of potassium, renin and angiotensin (Ang II). Consequently, concepts to explain autonomous aldosterone secretion as the basis for primary aldosteronism (PA) included the presence of stimulating autoantibodies to the Ang II type 1 receptor (AT1R), gain-of-function mutations in the AT1R and aberrant expression of G-protein-coupled membrane receptors that are responsive to alternative stimuli and have access to the cellular AT1R signaling apparatus (Luft, 2013, Mazzuco et al., 2010). However, while these ideas are great the power to explaining the pathophysiology of PA remained small. The breakthrough came with the systematic clarification of signaling pathways which control aldosterone secretion, the application of whole exome sequencing to adrenal disease and the discovery that a mutated channel which is associated with familial and sporadic forms of PA results in an increase in intracellular calcium (Fig. 1) (Choi et al., 2011). The same group also discovered that a mutation in *CACNA1H*, encoding the voltage-gated T-type calcium channel Cav3.2, is associated with an early onset form of primary hyperaldosteronism (Scholl et al., 2015). The data in the EBioMedicine paper by Daniil et al. strongly supports the disease-driving character of such mutations allowing calcium to influx more readily into the aldosterone-producing adrenal *zona glomerulosa* cell. And the paper adds familial and sporadic variants of PA with altered *CACNA1H* sequence to our knowledge database (Daniil et al., 2016). Systematic clinical work and modern genetic analysis combined with an elegant set of molecular, cellular and electrophysiological experiments helped the group to visualize a genotype-phenotype relationship. This relationship was apparent in clinical observations and detectable by means of in vitro investigations into channel properties, calcium signaling, steroidogenic enzyme expression and aldosterone secretion into cell culture supernatants. While the patients with a mild mutation did not, the subject with the severe *CACNA1H* mutation had early onset PA and multiplex developmental disorder. Interestingly, pathological neurologic features had been reported to occur in patients with PA due to a *CACNA1D* mutation which is also known to strongly affect intracellular calcium within *zona glomerulosa* cells (Scholl et al., 2013). The tumors of such patients are comparably small but show strong expression of aldosterone synthase and suppression of renin. Interestingly, it was suggested that some mutations may severely interfere with the cellular calcium homeostasis and even cause the death of an affected adrenocortical cell thus preventing the cell from developing hyperplastic or tumorous tissue.

However, less severe aberrations, including some mutations in the G protein-activated inward rectifier potassium channel 4 (GIRK4) potassium channel, seem to be associated with a milder phenotype of PA, larger tumors and expression of aldosterone synthase in the remaining normal *zona glomerulosa* tissue as a sign of non-(full) suppression of renin and angiotensin. This may explain why in tumors of patients with malfunctioning GIRK4 channels, the 11beta-hydroxylase is expressed at higher levels within the aldosterone-producing tumors and that such patients form more so-called "adrenal hybrid steroids" than patients with aldosteronomas due to *CACNA1D* mutations (Fig. 1) (Williams et al., 2016).

Along these lines, it seems to be very difficult to characterize the point of crossover from a single-nucleotide polymorphism to a mild disease-triggering mutation by means of such studies. An astonishing observation in this context is that mutations which are associated with the formation of aldosterone-producing adenomas were also observed in bilaterally hyperplastic adrenals and may even appear within different nodules in one adrenal gland although each nodule seems to harbour only one single mutation (Fernandes-Rosa et al., 2015). As such it remains open how channelopathies associated with PA – whether inborn or acquired – allow the affected adrenal cell to proliferate and break away from aldosterone-producing cell clusters in order to form aldosterone-producing adenomas.

So far, conventional cell culture studies did not provide the data to reach conclusions on how such mutations cause growth and

☆ Commentary on "CACNA1H mutations are associated with different forms of primary aldosteronism" by G. Daniil and MC Zennaro et al., France.

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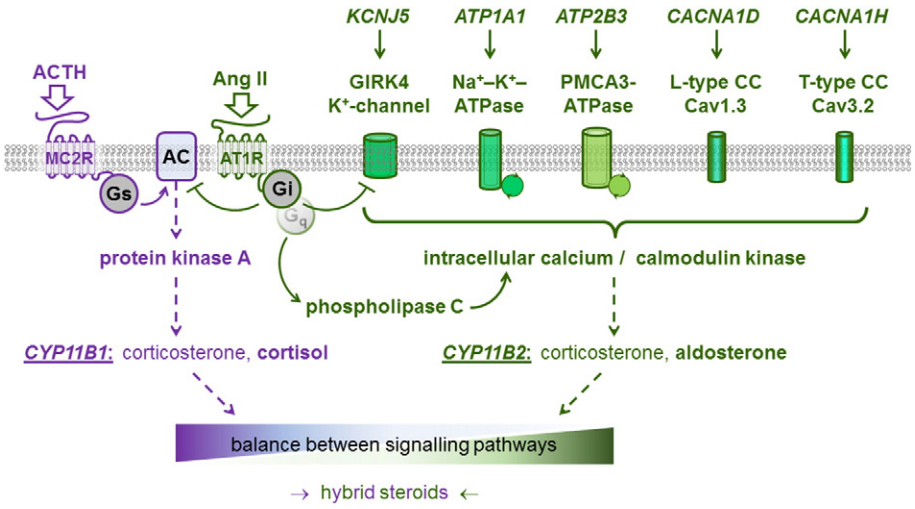

Fig. 1. Both, corticotropin (ACTH) and angiotensin II (Ang II) stimulate adrenal steroidogenesis via binding to their G-protein coupled receptors, MC2R and AT1R, respectively. Separation of glucocorticoid and mineralocorticoid synthesis occurs through different signaling pathways and suppression of the ACTH-stimulated adenylyl cyclase (AC) and protein kinase A activities when Ang II binds to its receptor. Ang II is generated when renin is secreted, leading to elevate intracellular calcium and expression of the aldosterone synthase (CYP11B2). However, the action of Ang II is bypassed in a state of hyperkalemia when potassium is prevented from efflux through the GIRK4 channel causing depolarization of the adrenal *zona glomerulosa* cell. This mechanism serves to regulate the organism's external potassium balance through an increase in aldosterone. Inherited or sporadic mutations in several ion channels that are employed in the regulation of the intracellular calcium concentration may lead to overactivity of calmodulin kinase and upregulation of CYP11B2, thereby achieving autonomy from control by renin and Ang II: primary aldosteronism. When aldosterone synthesis occurs independently from Ang II the influence of ACTH on steroidogenesis is conserved. Expression of both aldosterone synthase and 11beta-hydroxylase (CYP11B1) results in generation of so-called "adrenal hybrid steroids" which is dependent on the activity balance in the signaling pathways. This sketch is a further development of illustrations by Choi et al. (2011) and Zennaro et al. (2013).

proliferation of adrenal cortical cells. This may be because the influence of corticotropin, adrenal blood flow and tissue gradients also seem to play an important role in organ physiology and cell differentiation (Dringenberg et al., 2013). Therefore, while this study bridged the gap between clinical observations, the molecular background, its impact on cell physiology and aldosterone secretion, further such studies should address the question how the molecular changes promote cell proliferation and adrenal tumor formation.

Disclosures

The author declares no competing interest.

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