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COMMENTARY

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Role of adrenocorticotropic hormone in essential hypertension and primary aldosteronism

Decio Armanini MD[1] | Alessandra Andrisani MD[2] | Guido Ambrosini MD[2] | Luciana Bordin PhD[3] | Chiara Sabbadin MD[1]

[1]Department of Medicine—Endocrinology (DIMED), University of Padua, Padua, Italy

[2]Department of Women's Health-Salus Pueri, University of Padua, Padua, Italy

[3]Department of Molecular Medicine—Biological Chemistry, University of Padua, Padua, Italy

Correspondence
Decio Armanini, MD, Department of Medicine—Endocrinology, University of Padua, Padua, Italy.
Email: decio.armanini@unipd.it

Kobayashi and colleagues[1] investigated whether hormones other than aldosterone influence blood pressure (BP) levels in patients with primary aldosteronism (PA). They found a strong correlation between early and late morning systolic BP and morning adrenocorticotropic hormone (ACTH) in patients with aldosterone-producing adenoma (APA). The interpretation of these results could be disturbed by ongoing hypotensive treatment, since most patients with PA take calcium channel blockers, which could diminish circadian variation in BP, especially in patients with APA presenting with somatic mutations of calcium or potassium channels.[2]

The major physiological regulators of aldosterone production from the adrenal glomerulosa are potassium, angiotensin II, ACTH, and serotonin.[3] The aldosterone synthase (CYP11B2) activity is dependent on angiotensin II, but it is well known that acute ACTH administration increases plasma aldosterone.[4] The duration of ACTH administration is important since prolonged stimulation with ACTH suppresses aldosterone. This dichotomy is probably related to the different effect of ACTH on aldosterone synthase and 21-hydroxylase. The response of desoxycorticosterone (DOC) is only dependent on ACTH and the prolonged effect of ACTH leads to an occupancy of mineralocorticoid receptors (MRs) by excess of DOC associated with volume expansion and suppression of the renin-angiotensin-aldosterone system (RAAS). This effect is reproduced in the deficiency of 17α-hydroxylase (CYP17A1), which is associated with a suppression of the RAAS despite the lack of 17α-hydroxylase activity in the zona glomerulosa. In these patients, administration of dexametasone or of other corticosteroids normalizes ACTH and DOC and restores a normal function of the RAAS.

In recent years, the regulation of the effect of steroids has become more complex involving different enzymatic systems and in particular 11β-hydroxylase (CYP11B1), CYP11B2, 11-hydroxysteroidodehydrogenase (11-HSD) type 1 and 2, proteins binding to steroids, and peripheral metabolism steroids in fat and liver. Polymorphisms of these genes can modulate a slight increase in ACTH and aldosterone, despite the lack of these enzymes in the zona glomerulosa.[5] For example, polymorphism of CYP11B1, CYP11B2, and CYP17A1 could produce a defect of plasma cortisol and slight increase in ACTH, leading to restoration of cortisol concentration associated with an increased synthesis of aldosterone and androgens in the adrenals.[6] An increased activity of 5α-reductase at the level of fat could also increase the ACTH drive by relative deficiency of cortisol due to increased enzymatic conversion activity.[7]

Many patients with essential hypertension have suppressed plasma renin and normal-low aldosterone values. This finding is reported in many studies in China and Japan partly because of the increased sodium intake in these populations, but genetic factors should also be considered.[8] In the article by Kobayashi and colleagues,[1] for example, the controls with essential hypertension had a mean renin value of 0.4 ng/mL per hour and the aldosterone renin ratio was at the highest levels of normality. Low renin could also be due to an increased effect of cortisol related to a slight increase in ACTH. Some studies have found that patients with PA have a circadian rhythm of plasma aldosterone concentrations mediated by changes of ACTH.[9] Moreover, they reported that ACTH administration produced higher aldosterone concentrations in patients with PA compared with normal controls or patients with essential hypertension.[10] Diurnal increase of aldosterone in early morning and abolition of diurnal rhythm by dexamethasone confirms the role of endogenous ACTH as an important aldosterone secretagogue in PA.[11] Of note, Kobayashi and colleagues showed that early morning systolic BP was correlated with ACTH.[1] The hypersensitivity to ACTH is also present in some patients with essential hypertension, supporting the hypothesis that hypertensive patients who develop PA present some genetic or acquired predisposition linked to alterations of potassium or calcium channels or various hormone receptors.[3]

The actual interpretation of bilateral hyperaldosteronism is related to an increased sensitivity to angiotensin II, as demonstrated by the

marked response to stimulation with angiotensin II or to local production of angiotensin II. An alternative explanation is that some enzymatic alterations could slightly decrease plasma cortisol synthesis with a related slight increased production of ACTH, normalizing cortisol and increasing aldosterone values. We have recently proposed a possible link between low-renin essential hypertension, idiopathic aldosteronism, and unilateral adenoma, hypothesizing a progression from low-renin essential hypertension to bilateral adrenal hyperplasia, unilateral hyperplasia, and APA.[12] The permanent hyperstimulation of glomerulosa could lead to an autonomization of a part of the zona glomerulosa, leading to an autonomous adrenal adenoma producing aldosterone. A similar mechanism is involved in tertiary hyperparathyroidism or in ACTH-independent Cushing's syndrome due to adrenal lesions.

After the discovery of aldosterone, a strict opposite effect has been proposed for cortisol and aldosterone, considering cortisol as an anti-inflammatory and aldosterone as an inflammatory hormone. Since CYP11B1 and CYP11B2 genes are located in chromosome 8, it is possible to consider the involvement of ACTH in the regulation of the stress reaction and oxidative stress. This association is also proven by the strict similarity of type 1 MR and type 2 glucocorticoid receptor (GR) structure and their cooperation in the regulation of ACTH secretion. The hippocampus is very rich in MRs but lacks 11-HSD2 and therefore MRs are occupied by cortisol, regulating the fine circadian changes of ACTH. On the other hand, GRs seem to be involved in the regulation of cortisol in the early morning and in stress reaction.[13] It has been shown that mineralocorticoids have an effect at the brain level, considering that aldosterone is involved in many neurological diseases such as depression and psychosis.[14] The concept of strict regulation of MRs by the 11-HSD2 must therefore be revisited and include other factors that are involved in the preferential binding of cortisol or aldosterone to MR. For example, in mononuclear leukocytes, cortisol and aldosterone have a similar affinity for MR, but only the incubation with aldosterone is able to produce a mineralocorticoid effect, regulating the concentration of electrolytes and volume and increasing the expression of oxidative stress and inflammation-related genes. In fact, the incubation with cortisol does not produce inflammatory effects, while the incubation with canrenone can block the effect of aldosterone.[15]

Nongenomic effects of aldosterone should also be considered, cointeracting with the classical genomic effects. For example, a recent study found that aldosterone can produce damage in erythrocytes, which are anucleated cells, through the classical MR, and this effect is blocked by the coincubation with canrenone.[16]

The studies by Pitt and colleagues[17,18] have reported an evident effect of treatment with MR blockers in reducing the cardiovascular risk and relapse of cardiovascular accidents even in patients with normal aldosterone and renin values, supporting the important role of aldosterone in inflammation, heart hypertrophy and fibrosis. Prolonged treatment with MR blockers can not only antagonize the effect of aldosterone at the level of the MR, increasing the RAAS, but also can regulate the activity of some enzymatic steps at the level of the glomerulosa, reducing the secretion of aldosterone. A similar effect of spironolactone has also been demonstrated in the gonads.[19] The effect of MR blockers in the adrenals can also confirm the hypothesis that long-term treatment with MR blockers could reverse PA to essential hypertension.[20]

In conclusion, the progression of research indicates that the regulation of steroid secretion and effector mechanisms is complicated and these studies have implications in the better understanding of the pathogenesis, evolution, and treatment of essential hypertension and PA.

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