

# Regulatory Role of ACTH on Aldosterone in Aldosterone-Producing Adenoma

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## Article Info

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## ABSTRACT

Primary aldosteronism (PA), one of the most frequent causes of secondary hypertension, is mainly composed of two major subtypes: aldosterone-producing adenoma (APA) and bilateral hyperaldosteronism (BHA). In APA, ACTH plays a dominant role in the regulation of circulating aldosterone level, while in physiological condition and BHA angiotensin II has a stronger effect. This pronounced regulation of aldosterone by ACTH in APA causes a differential response of aldosterone to either ACTH stimulation or ACTH suppression in APA from that in physiological condition and BHA, and therefore, ACTH stimulation test can be informative in differentiating APA among patients with PA and essential hypertension. Histologic studies have suggested a possibility that the origin of APA especially consisting of clear, lipid rich cells could be zona fasciculata, rather than zona glomerulosa. Recent studies have been focusing on molecular classification among APA, which could lead to a better understanding of ACTH responsiveness in APA.

## Abbreviations

ACTH: adrenocorticotrophic hormone,

AII: angiotensin II

APA: aldosterone-producing adenoma,

AVS: adrenal venous sampling,

BHA: bilateral hyperaldosteronism,

MC2R: melanocortin 2 receptor,

PA: primary aldosteronism,

PAC: plasma aldosterone concentration,

StAR: steroidogenic acute regulatory protein,

ZF: zona fasciculata,

ZG: zona glomerulosa,

Primary aldosteronism (PA) is a pathological condition where aldosterone is over-produced from the adrenal gland either unilaterally or bilaterally, independent of the renin-angiotensin system which in normal condition is in charge of regulating aldosterone production<sup>1</sup>. PA is one of the most prevalent forms of secondary hypertension, and is considered to account for more than 5% of all hypertensives<sup>2-4</sup>. As a result of excess aldosterone, PA is clinically characterized by hypertension, high aldosterone/

renin ratio, and sometimes hypokalemia<sup>1</sup>. Detection of PA cases among hypertensive patients is essential because patients with PA have been known to be at risk of poorer cardiovascular and renal outcomes compared to those with essential hypertension even after adjustment for the blood pressure<sup>5,6</sup>.

Aldosterone-producing adenoma (APA) is a form of PA in which excess aldosterone is secreted from a benign tumor in the adrenal gland<sup>1,7</sup>. In this Mini-review, we focus on the role of adrenocorticotrophic hormone (ACTH) on blood aldosterone level in cases of APA and compare it to that in cases of other forms of PA.

### **Aldosterone-producing adenoma (APA) and bilateral hyperaldosteronism (BHA) are two major subtypes of primary aldosteronism (PA)**

PA has two major subtypes; aldosterone-producing adenoma (APA) and bilateral hyperaldosteronism (BHA)<sup>1,7,8</sup>. In APA, aldosterone is produced and secreted from a functional tumour usually occurring in the adrenal glands<sup>1,7,8</sup>. Aside from rare cases of APA which have functional tumours in the both adrenal glands, aldosterone production in APA is from one side of the adrenal glands on which the functional tumour resides. In contrast, BHA is a pathological condition where hyperplasia of both sides of zona glomerulosa of the adrenal gland occurs and autonomously overproduced aldosterone is secreted from both sides of the adrenal glands<sup>1,7,8</sup>. As factors causing hyperplasia in BHA are unknown, BHA is also known as idiopathic hyperaldosteronism (IHA). The differential diagnosis between BHA and APA is important since the treatment strategies for these two pathogenic conditions are different: APA can be surgically excised and cured, whereas BHA is usually treated medically with aldosterone receptor blockers<sup>7</sup>.

The currently accepted gold standard for the differentiation between APA and BHA is adrenal venous sampling (AVS)<sup>7-9</sup>. In AVS, blood samples are collected from left adrenal vein, right adrenal vein, and vena cava through a catheter usually inserted via the femoral vein, and the ratio of aldosterone over cortisol level in the samples is used for evaluation for the localization of the disease<sup>9</sup>. For those patients who seek surgical cure of APA, it is essential to perform AVS prior to surgery in order to confirm the diagnosis<sup>7</sup>. However, given the high expertise required to perform AVS<sup>9,10</sup>, and the consequent, limited capacity of AVS, it should be reserved for those highly suspicious of APA. Therefore, an easier and non-invasive diagnostic test has been looked for to select cases highly likely to have APA.

### **Differential regulation of blood aldosterone level in APA and BHA**

Under physiological conditions, the blood aldosterone

level is regulated mainly by angiotensin II (AII) and serum potassium level, and, to a lesser extent, by adrenocorticotrophic hormone (ACTH)<sup>1</sup>. ACTH is a pituitary hormone consisting of 39 amino acids and binds its specific receptor, melanocortin 2 receptor<sup>11</sup>, expressed by the adrenocortical cells. Upon its binding to MC2R, ACTH acutely activates intracellular cAMP-protein kinase A pathway, thereby increasing the expression of steroidogenic acute regulatory protein (StAR)<sup>12</sup>, which regulates the production of steroids<sup>12</sup>. In zona glomerulosa (ZG) of the adrenal cortex which is the major source of circulating aldosterone under physiological condition, upregulated StAR results in the increase in the production of aldosterone<sup>12</sup>.

Since 1970s, there have been reports which show there is a difference in the regulation of aldosterone between APA and BHA<sup>13-17</sup>. In BHA, the regulation of aldosterone by AII has been considered dominant rather than that by ACTH<sup>13</sup>, as in the case of normal subjects. However, in APA, ACTH is known to exert a stronger role to stimulate aldosterone than in the case of BHA and normal subjects<sup>14,15</sup>. Moreover, in APA, regulation of aldosterone by ACTH has been considered to be dominant over that by AII<sup>16,17</sup>, although some report that AII-responsive types of APA (AII-R APA) account for a considerable percentage of APAs<sup>18,19</sup>. The mechanism of the stronger effect of ACTH on aldosterone level in APA has yet to be fully unveiled: a paper showed a higher expression level of ACTH receptor in APAs<sup>20</sup>, but the causality has not been addressed.

The pronounced regulation of aldosterone by ACTH in cases of APA prompted us to think of ACTH stimulation test as a possible diagnostic test of APA and to examine the diagnostic efficiency of this test in a larger number of patients and in a more systematic way than earlier studies. In 2011, we reported that ACTH stimulation test after dexamethasone administration is a useful procedure to detect APA among those with suspected PA, with a high diagnostic accuracy<sup>21</sup>. We adopted dexamethasone administration the night before ACTH stimulation test in order to suppress endogenous ACTH and to minimize its effect<sup>21</sup>.

After our report, another group has performed a similar study analyzing the diagnostic capacity of ACTH stimulation test under dexamethasone suppression to diagnose APA, with the result consistent with ours in that the test is useful for detecting unilateral PA<sup>22</sup>. There have also been studies that tested the efficiency of ACTH stimulation test without dexamethasone suppression, but they were not so successful in differentiating the two major subtypes in PA patients<sup>23,24</sup>, suggesting the importance of dexamethasone administration. As shown in a previous study, dexamethasone administration can suppress the fluctuation of aldosterone level caused by endogenous

ACTH<sup>25</sup>, and may help to line up the baseline aldosterone level before ACTH administration.

We also thought of the possibility that there could be differences in circadian change and/or the change after dexamethasone administration of plasma aldosterone between APA and BHA. Hence, we examined circadian change in plasma aldosterone concentration (PAC), and changes in PAC after dexamethasone administration in patients with suspected PA, in order to evaluate the effect of endogenous ACTH on aldosterone secretion<sup>26</sup>. As expected, the change of blood aldosterone level in APA patients after dexamethasone administration was greater than those in IHA and non-PA patients<sup>26</sup>, indicating that aldosterone secretion in APA patients is more strongly dependent on endogenous ACTH than in BHA and non-PA<sup>26</sup>. In patients with BHA and non-PA patients, blood aldosterone levels showed circadian decrease towards the night but did not correlate with ACTH levels. This indicates that factors other than ACTH may cause circadian changes in aldosterone secretion in those patients. A report by Doi et al. demonstrated that mice lacking core clock genes, cryptochrome-1 and cryptochrome-2 showed the phenotype of BHA<sup>27</sup>, and this may suggest that clock genes are involved in the regulation of aldosterone production from the adrenal gland.

These two tests, ACTH stimulation test and dexamethasone suppression test, can be helpful in detecting cases highly likely to have APA, although they cannot be confirmative for the final diagnosis of APA because of the considerable number of cases of APA and BHA in which aldosterone does not respond as expected. However, they can be informative in choosing cases to be prioritised for AVS.

### Molecular stratification of APA can predict ACTH-responsiveness

From prior years, it has been known that there are several different cell types found in APA<sup>24</sup>. One type of the cells have little lipid storage in cytoplasm and morphologically resemble the cells in zona glomerulosa (ZG) of the adrenal gland<sup>28</sup>, which is the site of physiological aldosterone production under the regulation of AII<sup>28</sup>. Another type of cells have large amounts of intracellular lipid and are similar to zona fasciculata (ZF) cells<sup>28</sup> (ZF cells are responsible for producing and secreting cortisol, rather than aldosterone, in normal condition and express higher level of ACTH receptor than ZG cells). Also, a hybrid of the two types of cells above has been reported<sup>28</sup>.

There have been reports regarding the cell types and differential regulation in aldosterone production<sup>29</sup>. One report showed that APAs consisting of ZG-like cells are more responsive to angiotensin II than those consisting of ZF-like cells<sup>29</sup>. This may indicate different origins of APAs

consisting of these different cell types, because APA with clear, ZF-like, cells might be considered to develop from ZF, rather than ZG, given the morphological similarity and unresponsiveness to angiotensin II. Meanwhile, another paper demonstrated that angiotensin II responsive APA, mainly consisting of ZG-like cells, is as responsive to ACTH as angiotensin II unresponsive APA<sup>19</sup>.

Recently, researchers have been trying to understand the pathophysiology of APA on a molecular basis. Since the report by Choi et al in 2011 which identified somatic mutations of KCNJ5, a potassium voltage-gated channel, in some cases of APAs<sup>30</sup>, there have been numerous reports regarding somatic mutations in APAs and, in addition to KCNJ5, mutations of calcium voltage-gated channel subunit alpha 1D (CACNA1D; a calcium voltage-gated channel)<sup>31</sup>, ATP1A1 and ATP2B3 (ATPases)<sup>32</sup> have been identified in APAs so far. Phenotypic differences between those APAs with or without such mutations have also been reported, and nowadays, APAs have come to be characterised according to the somatic mutations they harbor. According to a report by Azizan in 2012, APAs with KCNJ5 mutation are more likely to consist of ZF-like, clear cells than those without KCNJ5 mutation<sup>33</sup>. A more recent study by Kitamoto et al. showed that APAs with somatic mutation of CACNA1D consisted mainly of ZF-like clear cells and blood aldosterone levels in these cases were more responsive to ACTH than those without the mutation<sup>34</sup>. Such molecular classification of APAs may provide a clearer image of the origin and the pathophysiological mechanism of APA in the near future. However, to identify mutations, samples of the APAs are inevitably required and, because the samples can only be obtained after surgical removal, the molecular classification of APA is only informative retrospectively, with limited capacity for prospective diagnosis in a clinical setup.

In conclusion, blood aldosterone level in APAs is more sensitive to ACTH than those in BHA and normal subjects, which is informative in the selection of those patients highly likely to have APA prior to AVS. Although the precise mechanism underlying this has yet to be unraveled, molecular classification of APAs depending on somatic mutations they have can be informative in understanding the pathophysiology of APAs.

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