Recent Advances in Hypertension

Aldosterone and Blood Pressure Regulation
Recent Milestones on the Long and Winding Road From Electrocortin to KCNJ5, GPER, and Beyond

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The purpose of this brief review is to highlight 3 recent conceptual advances in the ongoing exploration of the biology of aldosterone and how disorders of aldosterone metabolism and action lead to hypertension. Notably, important contributions to the advancement of our understanding in all 3 areas were published within the pages of Hypertension.

For >60 years, the link between aldosterone and hypertension has remained a key focus of research. The focus on this hormone and how it regulates blood pressure (BP) date back to a period of time when its putative existence, separate from that of glucocorticoids, was only speculated. The research intensity in the field accelerated with the initial report of the isolation of aldosterone (originally named electrocortin)1 in the early 1950s and the identification of its critical role in the early 1960s. Since then we have seen a continuously accelerating trajectory of research intensity.

Advances in our understanding of the biology and pathobiology of aldosterone have been critical to our understanding of the mechanisms of hypertension and its management. A PubMed search of this connection between hypertension and aldosterone demonstrates its ongoing importance. For listings through September 2013, the search strategy (hypertension OR blood pressure AND aldosterone OR mineralocorticoid) returned 514 references dating from 1948. Notably >10% of those reports (2031) have been published during the past 3 years, a testament to the ongoing importance of this area of research.

From this quantitatively and qualitatively impressive body of scholarship, I have identified 3 themes that I believe represent significant advances in our understanding of the link aldosterone and hypertension taken from studies published during the past 3 years in Hypertension and in other high impact journals. They are the following:

1. Emerging concepts related to the mechanisms by which aldosterone mediates its cardiovascular effects, especially those acting through rapid pathways
2. New insights into the mechanisms of aldosterone secretion, which impact on hyperaldosteronism syndromes
3. Advances in the management of resistant hypertension as they relate to aldosterone inhibition.

The Cardiovascular Actions of Aldosterone: Unappreciated Actions, Unappreciated Mechanisms of Effect

Until recently, the role of aldosterone in cardiovascular regulation and its mechanism of action in BP control were thought to be restricted to its renal effects. Aldosterone was widely seen as a hormone whose actions were predominantly related to renal sodium regulation and whose main mechanism of action was thought to be via regulation of transcription. However, during the past decade, important extrarenal, cardiovascular actions of aldosterone have been reported, viz. on vascular smooth muscle contractility, cardiac fibrosis, cardiac inotropy, and on growth- and death-regulatory mechanisms.2 Furthermore, beyond its direct transcriptional regulatory effects, aldosterone has been shown to trigger the activation of several second messenger signaling pathways traditionally associated with the activation of membrane receptors including regulation of cAMP metabolism, intracellular calcium concentrations, tyrosine kinases (both receptor and nonreceptor), and mitogen-activated protein kinases, especially the extracellular signal–regulated kinases.3

Studies during the last several years have elucidated the molecular mechanisms mediating at least some of these cardiovascular effects. Furthermore, a previously unappreciated receptor pathway mediating the vascular actions of aldosterone has now been uncovered.

The receptor basis of many of the actions of aldosterone is adequately explained by the activation of the classical cytoplasmic/nuclear mineralocorticoid receptor (MR) and by a direct transcriptional regulatory mechanism. Furthermore, some of the rapid (aka, nongenomic) effects of aldosterone have been clearly linked to activation of cytoplasmic MRs associated with the plasma membrane.4 However, it has long been speculated that some of the effects of aldosterone are mediated by a membrane-associated non-MR linked pathway.5 The identity of this receptor remained unknown until recently.

Studies during the last several years have clarified the receptor basis for vascular effects of aldosterone, both via MR-dependent and non–MR-dependent receptor mechanisms, and the importance of those mechanisms in the development of hypertension. McCurley et al6 demonstrated the importance of the classical MR for mediating vasopressor effects of aldosterone. Mice
with a smooth muscle cell (SMC)–specific genetic deletion of the MR demonstrated a blunted age–dependent increase in BP. Furthermore, as compared with wild-type–aged mice, the SMC-MR-deficient mice had decreased myogenic tone and blunted angiotensin-II–mediated vasocostriction. These data support an important role of SMC MR expression on BP regulation beyond renal effects of aldosterone.

Recent studies during the last 2 years have implicated G-protein–coupled estrogen receptor-1 (GPER; aka GPR30) in mediating MR-independent effects of aldosterone. GPER was first characterized as an orphan G-protein–coupled receptor. It was subsequently demonstrated to mediate some of the estrogen receptor–independent effects of estradiol.7 GPER is ubiquitously expressed including in vascular cells, both vascular endothelium cell (EC)4 and SMC.9 GPER activation mediates endothelial-dependent vasorelaxation.10 Furthermore, in vascular SMCs and vascular ECs, GPER activation stimulates proliferation and inhibits apoptosis.8,9 The initial demonstration of the GPER–dependent effects of aldosterone was in rat aortic vascular SMCs, where GPER was reintroduced (its expression being attenuated in primary culture). In this heterologous expression system, aldosterone potently stimulated apoptosis.9 This effect was inhibited by the selective GPER antagonist, G15. GPER–dependent effects of aldosterone were recently confirmed in rat aortic vascular ECs, a cell model with robust, persistent GPER expression, and minimal expression of the MR.8 In these vascular ECs, aldosterone potently stimulated apoptosis and inhibited proliferation with an EC50 in the pico-molar range. Both the potency of aldosterone and the directionality of its effects in ECs paralleled its actions in SMCs. Again, the effects of aldosterone were inhibited by the GPER antagonist, G15. Furthermore, downregulation of GPER expression using siRNA techniques attenuated the effects of aldosterone. Additionally, the endothelium-dependent vasodilator effects of aldosterone were shown to be GPER dependent.

The reports of GPER–mediated effects of aldosterone were initially viewed with skepticism by some commentators in the field.7 However, these findings have now been confirmed in other cardiovascular models. First, in human coronary microvessels, aldosterone modulation of angiotensin-mediated vasoconstriction was reported to be GPER dependent.11 Recently, aldosterone–mediated regulation of cardiac vagal tone was shown to occur via GPER activation.12 These data in total support an important role of GPER in mediating several of the cardiovascular actions of aldosterone.

**Regulation of Aldosterone Synthesis by Potassium Ion Flux: Disordered Mechanisms/ New Targets in Hyperaldosteronism**

Important advances have been made in our understanding of the regulation of adrenal aldosterone synthesis and the mechanisms underlying the phenomenon of autonomous aldosterone synthesis in hyperfunctional adrenal adenomas.

The major regulators of adrenal aldosterone synthesis are angiotensin II and plasma potassium ion concentrations. During the last several years, the mechanisms by which these factors regulate aldosterone synthesis have been elucidated.13 Adrenal glomerulosa cells, the site of aldosterone synthesis, are characterized by high resting potassium ion conductance, a phenomenon maintained by G-protein–activated inward rectifier K+ channels. Closure/inhibition of these channels, either related to angiotensin II type I receptor activation or hyperkalemia, leads to plasma membrane depolarization, activation of voltage gated calcium ion channels, and a consequent increase in intracellular calcium concentrations, which promotes the synthesis of CYP11B2 (aldosterone synthase) and thus aldosterone synthesis.14

Disordered regulation of both inward rectifying potassium channel function and aldosterone synthase expression has been linked to primary hyperaldosteronism syndromes. Familial hyperaldosteronism type 1 (glucocorticoid remediable hyperaldosteronism) has long been known to be related to disordered regulation of CYP11B2 expression; specifically because of the occurrence of a hybrid CYP11B2 gene under control of adrenal-bromocorticotropin rather than angiotensin II (and expressed in the adrenal zona fasciculata rather than the zona glomerulosa).15 Notably, a recent report in *Hypertension* identified the existence of an unappreciated adrenal micro-RNA (Micro-RNA 24) that regulated both CYP11B2 as well as CYP11B1 (11β-hydroxylase) and thus acted to modulate both aldosterone and cortisol production.16 The importance of this pathway either physiologically or as a potential therapeutic target remains to be established.

Of greater focus during the last several years has been the importance of the gene encoding the G-protein–activated inward rectifier K+ channel, KCNJ5, as a central actor in both the sporadic and the familial forms of primary hyperaldosteronism. After the initial discovery of a mutation in KCNJ5 in aldosterone-secretory adrenal adenomas from patients with familial adrenal hyperaldosteronism,17 there has been a flurry of studies in *Hypertension*. These reports have documented both the impact and prevalence of KCNJ5 mutations in hyperaldosteronism syndromes.18–20 Prevalence of these mutations has been reported in ≤41% of unselected patients with aldosterone-producing adenomas and may be more prevalent in females (≤50% prevalence).19

These studies in total have identified the critical role of potassium channel regulation of aldosterone synthesis and have significantly advanced our understanding of the basis for autonomous aldosterone synthesis in hyperfunctional adrenal adenomas.

**The Role of Aldosterone in the Presentation of Resistant Hypertension and the Role of Aldosterone Antagonism in Its Management**

Studies during the last several years have advanced our understanding of the mechanisms and management of resistant hypertension, that is, uncontrolled hypertension despite therapy with 3 drugs including a diuretic or BP elevations requiring ≥4 drugs for control. Admittedly this increased interest seems to be stimulated (at least in part) by the recent availability of new technologies to treat resistant hypertension by inhibition of the sympathetic nervous system, for example, with renal nerve denervation. However, recent reports have also emphasized the pathological importance of aldosterone in resistant hypertension. Furthermore, the mechanisms by which aldosterone antagonism may be effective in improving control rates in these difficult-to-treat patients have been clarified.

Aldosterone antagonism is now viewed as an important part of the management of patients with resistant hypertension. Primary hyperaldosteronism is more prevalent among patients with resistant hypertension than in the patient population.
general hypertension (in some studies ≈20%). However, even for the other 80%, increased aldosterone levels are a common consequence of the use of multdrug antihypertensive regimens, especially those including higher dose diuretics. The antihypertensive effectiveness of the aldosterone antagonist spironolactone was first reported >35 years ago. The use of spironolactone in the management of resistant hypertension, irrespective of baseline aldosterone levels, was first suggested more than a decade ago. However, the long-term use of this treatment strategy has only been established during the last several years. In their open label study population of 175 patients with resistant hypertension additionally treated with spironolactone for >1 year, de Souza et al reported further impressive BP reductions, averaging 16/9 mm Hg.

Spironolactone-mediated inhibition of central sympathetic nervous system activity has been suggested to be an important mechanism underlying its antihypertensive effects in patients with resistant hypertension. In a geriatric hypertensive population, inhibition of sympathoadrenal activity paralleled the greater BP-lowering effect of spironolactone (versus hydrochlorothiazide). Furthermore, aldosterone antagonism has been shown to block the diuretic-induced increase in sympathetic activity, an effect that may underlie the synergistic antihypertensive actions of this drug combination.

In animal models, the central administration of aldosterone has been shown to sensitize forebrain nuclei involved in cardiovascular control to the hypertensive effects of angiotensin II. In related studies, the same group demonstrated that the expression and function of both angiotensin II type I receptors and MR in the central nervous system were required for the development of hypertension in response to either aldosterone or angiotensin II. This pathway might be especially important as a mechanism by which aldosterone antagonism lowers BP. Thus in summary, aldosterone antagonism is being recognized as an important strategy in the management of resistant hypertension, acting in part by inhibition of central sympathetic outflow.

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References
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