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The Role of Aldosterone in Hypertension and Related Morbidities

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Abstract

Hypertension (HTN), and especially resistant HTN, is an endemic problem around the world with risk of end organ damage and increased rate of adverse effects despite treatment. Recent research has linked Aldosterone (Ald), the hormone responsible for sodium and water retention in the kidney, to resistant HTN in many cases. Aldosterone, part of the Renin-Angiotensin-Aldosterone System (RAAS), can be elevated beyond physiologic levels in many different disorders, and Primary Aldosteronism (PA) was recently shown to be the primary cause of secondary HTN. Further, Ald has known pleiotropic effects in other organ systems where there may be low levels of endogenous Ald production and functional mineralocorticoid receptors in the tissue. Specifically, Hyperaldosteronism (HA) has been linked to progression of chronic kidney disease, and pro-fibrotic, pro-inflammatory states in several different organ systems, especially the cardiovascular and hepatic systems. These effects by Ald on the renal, hepatic, cardiac, and vascular tissue suggest that novel treatment options for these patients. In cases where surgery is not viable to remove lesions creating the elevated levels of aldosterone, novel pharmacologic treatment should be explored, particularly targeting the Mineralocorticoid Receptor (MR) or Aldosterone Synthase (AS), which may be effective at preventing adverse outcomes in HTN patients, decreasing morbidity and mortality. This paper aims to explore in more depth the pathophysiologic role that hyperaldosteronism plays in HTN and future treatment options for such patients.

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Introduction

Systemic Arterial Hypertension (HTN) is considered a non-communicable condition and its prevalence rates are high in both developed and developing countries. HTN is the outcome of a complex interplay of both environmental and pathophysiological factors and is an extremely important modifiable risk factor for adverse cardiovascular events including and other diseases [1,2]. HTN is the major source of morbidity and mortality worldwide as it affects almost one-third of all adults over the age of 20 and the fact that high BP is a causative factor for increased risk of MI, heart failure, and kidney failure, which can all ultimately lead to death [3]. Studies suggest that aggressive Blood Pressure (BP) treatment reduces the risk of cardiovascular events but only about half (54%) of patients have their high HTN under control [4]. HTN leads to an increased risk of cardiovascular, renal, hepatic, and neurologic diseases including MI, stroke, hepatic fibrosis, and progression of CKD among others. However, very few of those patients with HTN are aware of their condition and are inadequately treated, which increases the global burden of disease and mortality [5]. HTN resistant to treatment is especially problematic for the increased burden it places on the healthcare system, with significant adverse events despite treatment. Patients with resistant HTN fail to achieve a goal HTN of less than 140/90 even with three or more antihypertensive medications of different classes at maximally tolerated doses. Resistant HTN is also particularly recognized because it places patients at risk of end-organ damage and is a major cause of stroke [6-8]. Obesity, increased age, and heightened Aldosterone (Ald) levels are directly correlated with increased likelihood of resistant HTN [9,10]. The prevalence of resistant HTN varies in the US drastically from study to study, but the indirect estimates range from 10% to 40% of all hypertensive patients have resistant HTN [9].

Primary Aldosteronism (PA) is a condition where Ald level is highly increased due to its autonomous production directly from the adrenal cortex. Autonomous Ald release causes the body to retain more sodium, water, induce hypokalemia and suppression of plasma renin. PA is the most common and a treatable form of secondary HTN [11,12]. Recent studies have shown a correlation between serum Ald level and increased BP in the general population, and even in the absence of

PA, blockers of its receptor, the Mineralocorticoid-Receptor (MR), are effectively antihypertensive in patients with normal range of Ald values [13]. Epidemiological studies show that HTN onset is strongly associated with salt consumption and there is a close relationship between average sodium salt intake and the incidence of HTN. Ald is now been known to mediate inflammation, autoimmune damage, oxidative stress, tubulointerstitial fibrosis in the kidney, and hepatic fibrosis. Excessive production of Ald promotes an inflammatory state promoted by T cell immunity. It can also induce an M1 macrophage inflammatory state and progression of liver fibrosis [14-16]. Ald is one of the important members of the Renin-Angiotensin-Aldosterone System (RAAS). Ald promotes sodium and water reabsorption and potassium excretion, and functions as a critical regulator of fluid and electrolyte homeostasis [17]. Hyperaldosteronism (HA) in particular has received significant attention in recent studies, where it is estimated that HA accounts for approximately 11% to 20% of resistant HTN patients [3]. This is important because recognition of HA-induced HTN could lead to novel treatment options for resistant patients that target either the Mineralocorticoid Receptors (MR) or more recently, research has looked into targeting Ald synthesis more proximally. This review will focus mainly on the role of Ald in the pathogenesis of HTN and related disorders.

Aldosterone

Ald, an important mineralocorticoid is primarily synthesized in the zona glomerulosa of the adrenal cortex by aldosterone synthase (AS, cytochrome P450 11B2, CYP11B2). MR is nuclear steroid receptors and is a member of the steroid receptor family of intracellular hormone-activated receptors. MR is expressed in renal epithelial cells. Ald binds to specific MR and Ald-MR activation induces expression of genes involved in sodium retention and traditionally participates in increasing blood volume and BP [18]. Aldosterone is one of the important members of the RAAS and is released upon stimulation by Angiotensin II (Ang II), serum potassium, dopamine production and Adrenocorticotropic Hormone (ACTH) by promoting activation of AS encoded by the CYP11B2 gene [19]. Ald promotes sodium and water reabsorption and potassium excretion, and functions as a critical regulator of fluid and electrolyte homeostasis [17]. Ald synthesis is induced in response to specific stimuli, including elevated potassium levels, Ang II, and Adrenocorticotropic Hormone (ACTH) release. These stimuli cause increased expression and phosphorylation of the Steroidogenic Acute Regulatory (StAR) protein, responsible for delivering cholesterol to the zona glomerulosa of the adrenal cortex [20]. Ald is then synthesized in the zona glomerulosa via the steroid biosynthetic pathway, which also produces cortisol and sex hormones. AS, on the CYP11B2 gene, completes the final 3 steps of Ald synthesis. The highly homologous 11ß- hydroxylase (CYP11B1) acts in parallel to synthesize cortisol, and abnormalities in both of these genes have been implicated in HA and subsequent HTN [21]. Most recently, we have generated a mouse model with transgenic human AS showed that fadrozole, an AS inhibitor could reduce Ald levels and high-salt diet-induced HT [22]. In humans, an analogous AS inhibitor, LCI669, has been studied and demonstrated a mild reduction in BP as well as a dose-dependent decrease in serum Ald levels [23]. However, at higher doses it was found that LCI669 loses its selectivity for CYP11B2, making it a poor choice for significant BP reduction in humans [23]. This finding highlights the need to find and study the safety and efficacy of more selective AS-inhibitors.

The other well-studied genetic abnormalities are two rare monogenic syndromes involving 11β-hydroxylase and AS that cause HTN. One of them is glucocorticoid remediable aldosteronism, caused by a chimeric gene that contains the 5′ promoter sequence of CYP11B1 and functional elements of CYP11B2, which results in Ald production under control of ACTH. Another one is 11β-hydroxylase deficiency with a chimeric gene containing a mutation in the intron 2 of CYP11B2, replaced with the homologous intron from CYP11B1 [24], which also correspond to increased levels of ACTH and subsequent 11-deoxysteroids, the precursor that leads to mineralocorticoid HTN [21].

Primary aldosteronism

Primary Aldosteronism (PA) is a group of disorders manifested by inappropriately high production of Ald, relatively autonomous from the renin-angiotensin system, which causes HTN, hypokalemia and increased sodium retention and is considered the most common treatable form of endocrine HTN [25,26]. In contrast to PA there is a different phenotype where a low renin activity in HTN exists but the plasma Ald concentration is apparently normal. This phenotype is considered unique from PA, termed Low Renin Hypertension (LRH), found in about 30% of hypertensive patients. PA is believed to be the most prevalent cause of LRH. PA is more prevalent than known before and has been described to be the most frequent cause of HTN due to increase in plasma volume and Ald-mediated constriction of systemic vasculatures. It is the major cause of secondary HTN with a high prevalence (~25%) in high risk populations [27-29]. Recent studies have revealed that PA is not only restricted to severe and resistant hypertensive patients; it can also be detected in mild to moderate hypertensive and in normotensive patients [30]. Individuals with PA experience worst quality of life, headache, vision problem, muscle cramp and fatigue. Although determination of plasma- Aldosterone to Plasma-Renin Ratio (ARR) is the gold standard for diagnosing PA, subsequent confirmation is performed with Adrenal Vein Sampling (AVS) and CT scan. Treatment options are dictated by the presence or absence of lesions with adrenal surgery (traditional Trans peritoneal or laparoscopic surgery) or therapeutic treatments with various MR antagonists [19,25,28,31,32]. Major causes of primary PA that can lead to HTN include Bilateral Idiopathic Adrenal Hyperplasia (BIH), adrenal adenoma, familial hyperaldosteronism type I (FHA-I), and 11ß-hydroxylase deficiency [33]. Adrenal adenomas, or benign tumors of the adrenal cortex, can lead to either Cushing's syndrome or PA but are typically easily corrected by surgical removal. Familial Hyperaldosteronism type I (FHA-I), a disease of autosomal dominant inheritance, is marked by Ald levels regulated by ACTH rather than Ang II *via* a chimeric gene as described earlier. FHA-I is also easily treated and is therefore also known as Glucocorticoid Remediable Aldosteronism (GRA) [26,29]. Finally, 11ß-hydroxylase deficiency causes adrenal hyperplasia and buildup of steroid precursors unable to make cortisol, which are then shunted to Ald pathway causing HA [21]. Multiple studies have focused on analyzing the data comparing treatment outcome with both surgical and pharmaceuticals treatment options these studies overwhelmingly resulted in the conclusion that no differences exist in terms of BP, serum potassium concentration or cardiovascular and renal outcomes, but the surgical procedures provided quicker benefits compared to pharmaceuticals like MR antagonists [28]. The beneficial results with pharmaceuticals, even though slower than surgical procedures, may provide an opportunity to develop newer MR antagonists with quicker onset as well as combination of therapy with other molecules to reduce the risk of side effect such as hyperkalemia.

Aldosterone pleiotropic effects

Kidney: Chronic Kidney Disease (CKD) is a slow and progressive loss of kidney functions over a period of several years. Kidney functions decline with aging, leading to increased prevalence of CKD in the patients over 65 years of age and high mortality. More than 30 million adults have CKD and millions of others are at increased risk in the US. Cardiovascular Disease (CVD) is the leading cause of more than 35% of deaths in the U.S. and majority of the CKD patients are at increased risk of CVD [35,36]. HTN, heart disease, and associated diabetes are the major cause of CKD leading to death for all patients with CKD. Sodium handling and water balance by the kidney are major determinants of BP changes, which may be mediated by the sympathetic nervous system, hormones and inflammatory mediators [37]. The kidneys play a central role in long term BP control, and high salt intake increases BP while reduced salt intake has beneficial effects in chronic kidney disease, although the precise mechanism of HTN has not been well understood [38,39].

HTN is related to more than 80% of patients with CKD and cardiovascular events, and a correlation exists between HTN and the nephropathy progressing to end-stage renal disease in humans. The kidneys are a critical regulator of BP, and Ald excess is a risk factor for progression of kidney disease [40,41]. Ald and its MR are well known controllers of BP by promoting renal sodium reabsorption and water balance. Ald and MR pathway signaling is closely related to dietary salt intake and excessive salt intake can cause MR activation. Further studies reveal that Ald plays a significant role in the development of salt-sensitive HTN and associated end-organ damage [38]. Based on this evidence, most of the available antihypertensive therapies are targeted to lower BP in an effort to control the progression of CKD, although hyperkalemia is a concern with the use of mineralocorticoid receptor antagonists [42]. This was supported by the recent results that MR antagonist, spironolactone, treatment produced significant reduction in BP, and liposomal clodronate treatment contributed to the attenuation of renal damage and inflammation along with partial reduction of interstitial fibrosis in the kidney [43].

In addition to hypertensive effects directly through renal sodium and water retention by high Ald, growing evidence suggests that excess Ald also induces endothelial dysfunction by activating pro inflammatory and pro fibrotic pathways which contributes to kidney pathogenesis such as renal hypertrophy, glomerulosclerosis, tubulointerstitial fibrosis, and vascular remodeling. The pro-inflammatory action of Ald has been reported in the kidney accompanied by an increase in TNF-α protein expression and IFN-γ mRNA expression level, which were significantly reduced by spironolactone [44-46]. Ald induced inflammatory response may culminate indirectly into promoting fibrosis. However, Ald plus salt treatment can directly induce fibrosis as evidenced by their increased production of pro-fibrotic matrix proteins CTGF, MMP2, fibronectin, macrophage infiltrate, TNF-α, an increase in kidney weight. These were reduced by MR antagonist spironolactone. The pro-fibrotic matrix protein CTGF is a key mediator of fibrosis and is up regulated in renal fibrotic diseases upon Ald stimulation through MR activation, since the fibrotic response was reduced by MR antagonist spironolactone. Taken together these results suggest protective effects of MR blockade in HTN-driven renal injury [43-47].

Recent studies have suggested renal tubular cell injury plays an important mechanism for the progression of CKD where Ald contributes to the progression of renal tubular injury. Inflammasomes are cytoplasmic multiprotein complexes that involved in the activation of caspase 1. Pyridine domain containing-3 (NLRP3) is the best characterized inflammasome and promotes the maturation of the pro inflammatory cytokines (IL-18 and IL-1b), mediating pathogenesis of renal tubular injury. Ald increases renal IL-18 production and suggest the possibility of inflammasome activation by Ald [48-51]. Ald stimulation of macrophages in vitro resulted in the activation of inflammasomes *via* the mitochondria-derived Reactive Oxygen Species (ROS). Ald infusion in mice (*in vivo*) resulted in tubulointerstitial damage along with increased expression of inflammasome NLRP3, caspase 1 activation, and increased IL-1b and IL-18 cytokine production. NLRP3 was significantly inhibited by the selective MR antagonist eplerenone and silencing NLRP3 by a siRNA. Infusion of Ald in mice with NLRP3 gene deletion remarkably improved albuminuria and podocyte damage [51-53]. These results demonstrate that Ald induces renal tubular injury and NLRP3 inflammasome plays an important role in mediating kidney injury induced by exogenous Ald, which opens a wide door for the evaluation of specific NLRP3 inflammasome and its combination with specific MR antagonist to combat renal tubular injury.

It is well known that the primary function of Ald is to act on the Na^+/K^+ pumps in the epithelial cells of the distal tubule of the nephron to increase sodium and water reabsorption, while inducing potassium secretion into the urine. Therefore, Ald works to ensure to a stable extracellular fluid volume. Ald is stimulated by Ang II, increased K^+ concentration, and acutely by ACTH release. More recently, it has also been found that Ald acts on Epithelial Sodium Channels (ENaC) and Sodium Calcium Exchange (NCC) channels. Specifically, ENaC and NCC expression increased in response to increased AS levels [22], which would lead to an expected further increase in sodium and water reabsorption.

Liver: High plasma Ald concentration has effects on epithelial and non-epithelial tissues and has been suggested to mediate inflammation, autoimmune damage, oxidative stress, endothelial dysfunction, and hepatic fibrosis [14,54,55]. Ald has direct profibrotic effects on the liver, mediated by the MR and oxidative stress, and can induce transcription factor Nrf2 and Nrf2-regulated genes that contribute to M1 macrophage inflammatory state and progression of liver fibrosis [56,57]. Ald binds to specific MR that are located in the cytosol of target epithelial cells and Ald-MR activation initiates an inflammatory response by increasing the generation of reactive oxygen species [58]. Ald promoted Hepatic Stellate Cell (HSC) activation, which increased expression of fibrotic markers: transforming growth factor beta (TGF-β), Plasminogen Activator Inhibitor-1(PAI-1), and collagen, and was partially reversed by Ald inhibitors [55].

Hepatic MR mRNA levels in hepatic stellate cells increased significantly and correlated with the expression of pro-inflammatory and pro-fibrotic genes. Furthermore, treatment with MR antagonist significantly reduced histological steatosis and attenuated liver fibrosis development in these NASH mice [59]. Pre-treatment with MR antagonist eplerenone attenuated serum Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Alkaline Phosphates (ALP), bilirubin and TNF-α levels, restored hepatic GSH to its normal level, and alleviated liver damage and tissue lesions demonstrated by histopathological assessment in CCl(4)-induced liver damage in rats [60]. Studies with Ald inhibitors have also shown that the MR antagonist reduces liver fibrosis in

pig serum-induced and bile duct ligated hepatic fibrosis in rats [55,61,62]. In cultured macrophages Ald induces M1 macrophage phenotype producing pro-inflammatory cytokines tumor necrosis factor alpha (TNF-α), Chemokine (C-Cmotif) ligand2 (CCL2) and CCL5 which promote the release of pro-fibrotic proteins, TGF-β) and PAI-1 [63]. Expression of both proinflammatory (MCP-1 and TNF-α) and profibrotic (Col1a1, Timp-1, MMP-2) markers as well as the expression of oxidative stress-associated genes (GSH reductase 1, GSH synthase and NRF2) were significantly increased in CDAA-fed NASH mice. Hepatic MR mRNA levels in hepatic stellate cells increased significantly and correlated with the expression of pro-inflammatory and pro-fibrotic genes. Furthermore, treatment with MR antagonist significantly reduced histological steatosis and attenuated liver fibrosis development in these NASH mice [59]. Pre-treatment with MR antagonist, eplerenone, attenuated serum Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Alkaline Phosphatase (ALP), bilirubin and TNF-α levels, restored hepatic GSH to its normal level, and alleviated liver damage and tissue lesions demonstrated by histopathological assessment in CCl(4)-induced liver damage in rats [60]. Studies with Ald inhibitors have also shown that the MR antagonist reduces liver fibrosis in pig serum-induced and bile duct ligated hepatic fibrosis in rats [55,61,62,64].

Heart: Several animal models have shown a link between HA and cardiac remodeling, specifically collagen remodeling leading to fibrosis and Ventricular Hypertrophy (LVH) [65]. One study also demonstrated a significant positive correlation between LVH and primary aldosteronism in human patients who were age, sex, systolic BP, and BMI matched [66]. It is believed that increased. Ald contributes to oxidative stress and inflammation in the myocardium as well as other organ systems, which leads to a fibrotic response and subsequent remodeling [67,68]. LVH remodeling was independent of changes in BP and was prevented with low doses of spironolactone (below antihypertensive doses) [65]. There has been mixed evidence for the dependence of this remodeling on salt-intake. Some findings indicate that cardiac and renal remodeling only occur in the presence of a high salt diet [66], while at least one study found that HA can lead to cardiac remodeling in a normal salt setting [69]. Interestingly, these rats responded better to spironolactone treatment compared to their high salt counterparts to reduce cardiac incidents [69]. HA has been associated with higher incidences of CVD compared with BP matched essential hypertensive patients. Specifically, nonfatal MI, stroke, and a trial fibrillation were 6-fold, 4-fold, and 12-fold higher in the HA patients, which included both adrenal adenoma and idiopathic HA patients [70]. Interestingly, one of the results from the Framingham study found that increased Ald was related to establish CVD risk factors in a complex fashion, including direct correlations to female sex, diuretic treatment, and serum total lipoprotein-to-HDL cholesterol ratios [71]. This finding was confirmed by another study showing serum Ald levels were also significantly associated with serum triglyceride, as well as waist circumference [72]. Blocking Ald effects with MR antagonists, eplerenone and spironolactone have been shown to be effective for HTN and heart failure [73]. It has been shown that inhibition of MR reduces the incidence of heart attack, stroke, and mortality in addition to controlling BP [74]. Additionally, it has been demonstrated that blockade of Ald signaling could inhibit inflammation, cardiovascular remodeling, and atherosclerosis [75].

Vasculature: Although Ald and MR are important in regulating BP by promoting renal sodium reabsorption and water balance in the kidney, the vasculature also plays an important role in contributing to the development of HTN and controlling of BP. In addition to renal epithelial cells, MR is also expressed and fully functional in the Endothelial Cells (EC) and Vascular Smooth Muscle Cells (VSMC) of the human vasculature which contributes to vascular contraction and myogenic tone. MR in both EC and VSMC are responsive to exogenously administered aldo and could contribute to BP regulation by modulating vascular reactivity and tone [76-79]. Ald synthesis may not be restricted to adrenal glands but be locally produced in several extra-adrenal tissues: cardiac, renal and vascular. Vascular endothelial cells express aldosterone synthase (CYP11B2) and are capable of producing low levels of Ald [80]. Ald-induced vascular dysfunction was inhibited by MR antagonist along with reduction of Reactive Oxygen Species (ROS), and increases in Superoxide Dismutase (SOD1) and Soluble Guanylyl Cyclase (sGC) [81]. These results suggest that MR antagonist spironolactone may provide improvement in Ald-induced vascular endothelial dysfunction by reducing oxidative stress and up regulating antioxidant systems and may regulate HTN and BP control.

Similar to the effects on cardiac tissue, the vasculature experiences inflammatory, fibrotic, and hypertrophic changes in response to HA [68]. This stiffening decreases the vasculature's ability to respond to adrenergic stimulation [21]. In one RCT comparing eplerenone and atenolol, only eplerenone, a selective Ald MR inhibitor was found to reduce both arterial wall stiffening and the collagen/elastin ratio to levels similar to normotensive patients [82]. The mechanisms by which Ald affects vasculature are multiple, including reduction of nitrite oxide availability, direct effects on Glucose-6-Phosphate Dehydrogenase (G6PD) and Epidermal Growth Factor (EGFR) to increase cell swelling and stiffness, and decreasing the functional capacity of epidermal progenitor cells [83]. For a comprehensive review of the mechanisms by which Ald exerts its effects on the vasculature, see the review written by Briet and Schiffrin [83]. It is believed that the evolutionary reason for these changes are to allow the vasculature to support the stresses associated with a chronically hypertensive state [21].

Aldosterone-to-renin ratio (ARR) as indicator

Aldosterone-to-Renin Ratio (ARR) is the most sensitive means of differentiating primary from secondary causes of hyperaldosteronism and has become the new primary screening and diagnostic tool for HA-associated HTN. In PA, as Ald secretion rises, the rate of production of Ang I from endogenous angiotensinogen in *ex vivo* testing should fall because of sodium retention. However, despite many benefits of using this measurement including its decreased susceptibility to normal daily fluctuations, the definition is not yet fully agreed upon, creating significant disparities in estimates of the prevalence of an altered ARR in hypertensive patients [68]. The different definitions include: increased ARR, increased ARR with decreased plasma renin, and increased ARR with decreased renin and increased Ald, which lead to an estimated prevalence of 5.9, 2.6, and 0.2% respectively [68]. While elevated ARR remains the number one cause of secondary (non-essential) HTN [21], reliance on ARR as the primary diagnostic criteria has a tendency to overestimate the contribution of HA specifically [84]. Despite these problems, elevated ARR remains a good indicator for disease states. Specifically, ARR is strongly correlated with increased risk of HTN and BP progression to further stages according to the staging set by the JNC VI [85].

Salt sensitive hypertension

It has been demonstrated many times that the link between

increased Ald and HTN is a high-sodium diet. In human AS transgenic mice, those with altered AS and a high salt diet developed HTN, in contrast to both the WT mice that showed no salt-sensitivity, and the normotensive mutant mice on low sodium diets [22]. Additionally, N-terminal proatrial natriuretic peptide (NT-ANP) levels, a salt-secreting peptide hormone released by the cardiac atria, were found to be inversely correlated with salt sensitivity [86]. Taken together, high Ald and low NT-ANP in an individual may indicate salt-sensitivity in an individual. Of note, MR activation can occur in the absence of HA, which may also lead to salt-sensitivity and HTN. This has been observed in the settings of obesity, diabetes mellitus, chronic kidney disease, and polycystic ovarian syndrome [87]. The mechanisms by which salt-sensitivity occurs in these cases are believed to be either increased MR transcription or translation, increased sensitivity of MR, or MR activation by other hormones [87].

Current opinion classifies salt-sensitive HTN into three subgroups. First is low renin salt-sensitive HTN, which is characterized by non-elevated but inappropriate levels of Ald given the Ang II levels. Patients belonging to this subtype tend to respond best to diuretics compared to RAAS-acting drugs [21]. The second group is termed "non modulators" for their normal-high renin levels and their inability to decrease Ald levels in response to high sodium intake [21]. In their review paper, Freel and Connell suggest a third group, the elevated ARR, to be separate from the first two, possibly existing on a spectrum of disease progression from low-renin HTN to non modulator HTN and finally to elevated ARR HTN [21]. However, they suggested the need for longitudinal studies to confirm this hypothesis.

Resistant hypertension and treatment options

Ald appears to play an important role in resistant HTN, defined as HTN not controlled on 3 different antihypertensive agents, including diuretic. Several studies have now demonstrated that HA is especially prevalent in resistant HTN (14% to 21% of patients) compared to the general HTN population and that as the severity of HTN increases, the incidence of HA does also [88]. This suggests that a good percentage of resistant HTN cases could benefit from treatment that targets Ald and its mediators.

1. Specifically, spironolactone, a non-selective MR antagonist, has been demonstrated to be highly effective at reducing BP in multiple different studies with resistant HTN patients. For a summary of these studies, which estimated a mean decrease in BP of 25-16/12-9, see the review written by Clark et al [88]. Surprisingly, spironolactone treatment was found to be effective in resistant HTN patients regardless of their serum Ald levels. While the efficacy in treating HA-associated HTN is obvious, the effects that spironolactone would have on other resistant HTN patients is less so. Possible explanations for this BP-reducing effect in non HA patients includeTissue levels of Ald are much higher than serum levels would indicate,

2. Non-genomic effects of Ald acting outside MR activation, and

3. Cortisol or other hormones are also stimulating MR receptors [88].

It is likely that the reason for this is a dual action of spironolactone. In HA patients, the primary effect is its diuretic actions in the kidney, while in patients with normal HA the predominant factor in lowering BP is the effect spironolactone has in reducing vascular resistance [88]. Additionally, spironolactone, when given in combination with the conventional treatment, was found to reduce mortality by 30% in patients with advanced cardiac failure, signaling that spironolactone treatment not only reduces BP but also decreases the rate of adverse outcomes related to HTN-associated morbidities [89].

Eplerenone, an Ald-specific MR blocker, has also been proven useful for treating HTN-associated outcomes in many recent studies. Treatment with eplerenone following an acute MI saw a 15% decreased mortality rate compared with the standard of care [90]. Further, eplerenone has been shown to decrease adverse events in patients with chronic HF and reduced LVEF and decrease the overall rate of hospitalizations in patients with chronic HF [89]. Because eplerenone is a potassium-sparing diuretic, its use in patients at risk of developing hyperkalemia or kidney disease has been more controversial. In one study, renal impairment was similar between the two groups, but hyperkalemia was twice as prevalent in the eplerenone treated group compared with placebo [91]. Further evaluation of the study found that while eplerenone did create a moderate increase in hyperkalemia, it did not contribute to a rise above 6.0 mmol/l and that when closely monitored in at-risk patients; eplerenone was still safe and efficacious at reducing hospitalizations and mortality related to HF and other CV events [92]. While these results are promising, the increased rate of hyperkalemia still indicates a use for the development of newer, safer, Ald-specific MR antagonists.

Finally, more recent research has looked into blocking AS an alternative to MR-blockers for reducing Ald-associated HTN. Mouse models have shown promising results, effectively lowering HA and salt-sensitive HTN with the treatment of fadrozole, an AS-inhibitor [22]. As mentioned previously, the analogous drug, LC1669, showed mild reductions in BP and circulating Ald levels, but at higher doses lost selectivity and also began acting upon CYP11B1 [23]. Again, a promising route for future drug research is in the development of a more selective AS inhibitor which could potentially have significant effects on BP reduction in resistant cases as well as effects the mitigate the dreaded cardiovascular and renal complications associated with HA-related HTN.

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