Interplay of Aldosterone, Sodium, Metabolic State, Inflammation and Oxidative Stress

An interesting example of the relationship between aldosterone, sodium status, and pathologic cardiac remodeling is found in comparing the Yanomami tribe of South America to people of industrialized countries. The Yanomami subsist on a high potassium/low sodium diet and have high circulating aldosterone levels, yet no increased risk of hypertension or vascular damage.[1] In industrial societies, where diets are often high in sodium, aldosterone levels (even when within the reference interval) are significantly associated with hypertension, chronic kidney disease, obesity, high circulating triglyceride concentrations, and the metabolic syndrome.[2] In a 4-year study that followed randomly selected subjects from the general community, aldosterone was a predictor of new onset hypertension, central obesity, and type-2 diabetes mellitus.[3] In this study, aldosterone was not, however, predictive of either development of concentric left ventricular hypertrophy or heart failure. Nevertheless, aldosterone appears to be a significant player in cardiovascular, renal, and metabolic diseases of man, which are major causes of morbidity and mortality and economic burden in the developed world. Similar large-scale epidemiologic studies have not been performed in companion animals. A disordered relationship between sodium status and aldosterone levels has been linked to the pathologic remodeling and dysfunction of target organs in experimental animal models (Supplemental Table 1). Although it comes as no surprise that increased aldosterone levels and normal or elevated total body sodium levels lead to fluid retention, systemic hypertension, and hemodynamic overload, the direct relationship between aldosterone, sodium intake, and pathologic cardiovascular remodeling was a novel finding with therapeutic implications.

Obesity likely contributes to pathologic remodeling via aldosterone production and potentiation of inflammation and oxidative stress. Increased adiposity enhances aldosterone excess by secreting aldosterone-releasing factor and a positive correlation between body mass index and aldosterone levels has been documented in people.[4,5] More recent work has shown that adipocytes possess aldosterone synthase and are regulated by Ang II.[6] The increase in circulating aldosterone associated with obesity is likely, due to both increased secretion from the adrenal gland and local release from adipocytes.[2,7] It has also been shown that adipocytes, via release of cytokines, contribute to increased generation of ROS and increased inflammation.[8] Increased ROS (even in the absence of high sodium levels) may directly, and independently activate the MR or activate the glucocorticoid-MR complex.[9],[10] To compound this deleterious cascade, the MR is also present in adipocytes and excess MR stimulation has deleterious effects on the biology of adipocytes.[7] Two examples include the decreased thermogenesis of brown fat and stimulation of release of proinflammatory adipokines from white fat. An animal model of the metabolic syndrome (a derivative of the spontaneously hypertensive rat with a leptin receptor mutation and increased aldosterone production), provided further evidence for MR-upregulation as a mediator of pathologic remodeling.[11] In this study, a high sodium diet led to systemic hypertension, proteinuria, glomerular podocyte damage, and increased biomarkers of renal injury, despite a reduction in serum aldosterone concentration. The relationship between sodium status and circulating aldosterone levels therefore changed in an appropriate manner, likely due to feedback mechanisms. Despite this change, however, gene expression patterns reflected MR-upregulation. Furthermore, the renal damage was ameliorated by the MRA, eplereonone. Investigation into the mechanism of MR-upregulation despite reduced aldosterone production implicated oxidative stress leading to MR activation, as the anti-oxidant tempol reduced salt-

evoked MR-upregulation, proteinuria, and kidney injury in a rat.[11] Rodent models have likewise demonstrated that increased oxidative stress, due to a hyperactive RAAS, also impacts metabolic status by decreasing insulin release and sensitivity. Proposed mechanisms include 1) hypokalemia resulting from increased aldosterone activity directly decreasing pancreatic insulin secretion and 2) increased ROS generation leading to impaired glucose-stimulated insulin secretion.[12,13] Furthermore, MR activation has been shown to impair insulin sensitivity in adipocytes and skeletal muscle, whereas MR blockade restores insulin sensitivity.[14,15] The clinical impact of MR blockade in restoring insulin sensitivity in people and animals with diabetes has yet to proven.[16-18] Finally, oxidative stress and inflammation (and therefore RAAS activation) are also suspected to accelerate the biological aging process. The leukocyte telomere length (LTL) has been used as a register of chronically accruing inflammation and oxidative stress with a shorter LTL indicating greater cell turnover and telomere attrition.[19] On average, the LTL is decreased in people with chronic CHF when compared to an age and gender matched cohort.[20] An increased renin to aldosterone ratio has been associated with shorter LTL in a cohort of Framingham study participants (including hypertensives), whereas higher aldosterone concentrations have been correlated to shorter LTL in men with systemic hypertension.[21,22] In summary, the mechanisms by which sodium, adiposity, inflammation, and oxidative stress potentiate aldosterone and MR-induced cardiovascular and kidney damage are complex and multiple.

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