Editorial Commentary

Unraveling the Mechanism of Renin-Angiotensin-Aldosterone System Activation and Target Organ Damage in Hypertensive Blacks

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The International Society on Hypertension in Blacks consensus statement in 2010 noted that, in the setting of high dietary sodium intake, hypertensive blacks have particularly impressive responses to renin-angiotensin-aldosterone system (RAAS) blockade.1 The statement went on to point out that the excessive target-organ damage (TOD) in hypertensive blacks can be attributed to RAAS activation. Although a normal-to-“high-renin” hypertensive state is most prevalent, the classic hypertension literature has categorized blacks as typically having a “low-renin” state.2 There is somewhat of a paradox in the observation that blacks, despite having a low-renin state, have high serum aldosterone concentrations.3 Blacks experience disproportionately higher rates of hypertension-related TOD compared with whites.4 The mediators of the higher rates of TOD noted in blacks are most likely directly attributed to high levels of downstream mediators of the RAAS, such as aldosterone and angiotensin II. The mechanism by which a low-renin state can be associated with such an apparently active RAAS is not clearly defined.

The article by Michel et al,5 in this issue of Hypertension, addresses the mechanism by which RAAS activation affects blood pressure (BP) regulation in a population of African ancestry. Specifically, the authors evaluated plasma renin, plasma angiotensinogen (AGT), and serum aldosterone concentrations in 579 South African blacks. They demonstrated an inverse relationship between plasma renin concentrations and BP (P<0.001) on one hand, as well as plasma renin concentrations and dietary sodium intake (24-hour urinary Na+/K+, P<0.0001) on the other hand. Despite this inverse relationship, there was a direct and independent association between AGT concentrations and systolic BP (P<0.005) in a subset of participants with urinary Na+/K+ at or more than the sample median (proxy for high sodium intake). Furthermore, in this same subset, there was an independent and direct relationship between AGT and serum aldosterone concentrations (P<0.0001). This observation was strengthened by the incremental increase in the multivariate-adjusted relationship between AGT and both serum aldosterone concentrations and systolic BP across tertiles of urinary Na+/K+. These impressive relationships were not observed in the subset of participants with urinary Na+/K+ less than the sample median.

The primary function of circulating AGT is to act as a substrate for renin, resulting in the biologically active peptides angiotensin I and angiotensin II. It is important to appreciate that the Michaelis-Menten constant for the renin-AGT reaction approximates the concentration of circulating AGT.6 Therefore, AGT concentrations, as opposed to renin concentrations, may be the rate-limiting factor in the generation of angiotensin I. Angiotensin II subsequently stimulates aldosterone secretion downstream in the RAAS cascade. Although the relationship between AGT and BP has been established for several decades,7 the mechanism has not yet been definitively elucidated. This study, to the best of our knowledge, is the first to demonstrate a relationship between AGT and serum aldosterone concentrations and BP in an environmental milieu of high dietary sodium intake, shown to be inversely associated with plasma renin concentrations. Aldosterone is an important mediator of TOD in hypertensive patients via a complex process that involves tissue fibrosis (myocardial and renal), inflammation, and loss of vascular reactivity.8 Dietary sodium intake and aldosterone may act in concert to accelerate TOD.9 The findings of Michel et al10 demonstrate that, in the particular situation of high dietary salt intake, despite the tendency to have a low-renin state, AGT participates in BP regulation in hypertensive black patients. This finding argues strongly for the need to control for dietary sodium intake in future studies evaluating the effects of RAAS on BP regulation in hypertensive blacks.

Several questions still remain to be addressed. First, whereas previous studies have alluded to the association of the AGT gene and BP regulation in populations of African ancestry,10,11 Michel et al5 in an attempt to study determinants of AGT, were not able to demonstrate the role of the AGT genotype in explaining the relationship among AGT, aldosterone, and BP. This is not entirely surprising given the limitation of the cross-sectional design of this study. Second, only approximately half of the study population was hypertensive, which is important to appreciate given the alteration
of the renal-pressure-natriuresis mechanism in hypertensive patients. Evaluation of a purely hypertensive cohort with a similar study design may mitigate this issue. Third, there is also the possibility of dysregulation in the production of AGT that was not addressed by Michel et al. It is important to consider the possibility of independent adipocyte secretion of aldosterone, an especially important consideration in blacks in whom obesity is prevalent. Fourth, and perhaps most importantly, the study by Michel et al fails to address the impact of the tissue-specific renin-angiotensin system and its contribution to circulating AGT. This is a very active area of hypertension research. Finally, the generalizability of findings from this study must be taken in the context of its cross-sectional design. Even within ethnic/racial groups there is considerable variability in the levels of and expression of key actors of the RAAS cascade. Despite these limitations, we applaud the findings from this study as an important contribution to the discussion on mechanisms of the RAAS activation as a major factor in contributing to the devastating toll of hypertensive disease in populations of African ancestry.

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References
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