Editorial Commentary

Sensitivity to Aldosterone
Plasma Levels Are Not the Full Story

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In this issue, Tu et al1 show clear differences in sensitivity of blood pressure (BP) to aldosterone between blacks and those of predominantly white ancestry, in both children and adults. It has long been known that blacks are more salt sensitive than whites; this contribution thus complements the previous findings and has ramifications for the role of aldosterone across the board. The article reports the unusual combination of a long-term (>20 years) observational study on children aged 5 to 17 years starting in 1986 and an acute intervention study comparing the effects of fludrocortisone administration for 2 weeks on BP, weight, and hormonal parameters in black and white adults.

The long-term study enrolled 580 children (266 blacks, 314 whites). Age, height, weight, systolic and diastolic BP (DBP), concentrations of plasma electrolytes (Na⁺ K⁺), plasma aldosterone (PAC), and renin activity (PRA) were measured, plus urinary excretion of Na⁺, K⁺, and creatinine. At baseline, black children were on average 18 months older, with a higher body mass index and slightly but significantly higher BP (103/43 versus 100/41 mm Hg). They also showed significantly lower PAC (9 versus 14 ng/dL) and PRA levels (2.8 versus 3.3 ng/mL per hour), with indistinguishable plasma [K⁺] and overnight urine excretion levels of K⁺ and Na⁺.

In the subsequently re-enrolled adult subcohort, the blacks were 17 months younger, with higher body mass index (31 versus 28) but identical systolic and DBP (116/74 mm Hg). They had lower levels of PRA (1.0 versus 1.5 ng/mL per hour) and PAC (5 versus 9 ng/dL), with levels of plasma K⁺ and BP indistinguishable from those in whites. Urinary Na⁺ excretion was similar (78 versus 81 nmol/mg creatinine), but K⁺ excretion was lower (18 versus 21 nmol/mg creatinine).

Using varying coefficient regression analysis, the authors estimated the effects on systolic BP of increasing PAC as a smooth function of PRA. The plots are strikingly dissimilar, in both children and adults. For whites the estimated effect of PAC on BP as PRA increased is a barely discernible apparent rise (P=0.16); in contrast, in blacks, the effect was highly significant (P=0.004) and became even stronger at low PRC levels.

The intervention study provided direct evidence for enhanced sensitivity to mineralocorticoid receptor (MR) activation in blacks, to complement the highly suggestive differences both at baseline and 20 years later in the longitudinal study. After 0.2 mg/d of fludrocortisone for 2 weeks, BP and weight in whites were unchanged; in blacks, BP rose by 6 mm Hg and weight by 1.5 kg. PRA decreased in both groups, to a similar extent; PAC similarly decreased, but in whites by 11 ng/dL, more (P=0.014) than in blacks (4 ng/dL). Baseline PAC values are not shown but are presumably higher for both groups than the 9 and 5 ng/dL found in the re-enrolled adults. Absent baseline values, it is conceivable, but not likely, that the falls may represent similar percentage changes in both groups, for example, 6 to 2 ng/dL in blacks and 16 to 5 ng/dL in whites. For this to be the case, baseline PAC values would need to be considerably higher, particularly in whites, than in the pre-enrolled subjects.

Where does this leave us? It seems indisputable that blacks have significantly lower PAC levels as children and adults. Second, it seems indisputable that blacks are more sensitive to MR activation, by aldosterone physiologically or fludrocortisone experimentally, than whites: the extent to which the BP rise reflects volume expansion and effects on CNS/vascular wall remains moot. The lesser absolute, and probably percentage, fall in PAC in blacks is somehow counterintuitive, in terms of sensitivity to MR activation, particularly given the similar decrease in PRA in the 2 groups, and the 0.2 meq/L lower (P<0.001) plasma [K⁺] in blacks, with no change in whites.

And now for mechanisms and implications. In 1991, Wilson and Grim2 put forward an hypothesis that the higher prevalence of hypertension in blacks might reflect residual selection pressure from transatlantic transportation from West Africa favoring those with higher levels of sodium retention. This was followed by an endorsement by Diamond,3 and in short order by a torrent of criticism sometimes bordering on abuse, often from critics apparently innocent of the ability to distinguish hypothesis from fact or selection pressure from genetic difference. As an hypothesis it is attractive, impossible to prove, and almost equally so to disprove.

The point of departure of the Tu et al1 study is “Blacks in comparisons to whites have disproportionately more hypertension, and suffer complications at a higher rate. Central to the etiology of the hypertension appears to be retention by the kidney of additional sodium.” There is a chicken and egg dimension to the second sentence—is increased sensitivity to aldosterone the driver, does something else drive increased sodium accumulation which lowers PRA and PAC, or do both...
mechanisms coexist? If renal, and by extension other epithelial, MRs are supersensitive to aldosterone, this may reflect differences(s) at any point in aldosterone action—in the receptor itself, for which there is no evidence, or in MR interactions with other, G-protein–coupled receptors, coactivators, and coregulators, or nuclear regulatory elements, for all of which again there is little if any evidence. The shadowy presence of endogenous ouabain, elevated in hypertension, secreted in response to adrenocorticotropic hormone, angiotensin via AT1 receptors, and sodium loading adds to the complex possibility and would provide a mechanistically coherent explanation. Finally, >50 years ago sodium-deficient adrenalectomized sheep were shown to be much more sensitive to infused aldosterone than when sodium replete, in terms of changes in parotid salivary Na+/K+ ratio.4 In the study under review, the situation is the opposite: the black subjects seem to be sodium enriched but to have increased sensitivity.

If sodium hyper-repletion per se rather than differences in MR and MR-associated effector mechanisms underpins hypersensitivity to aldosterone, what are the drivers of this different state of Na+ balance? Are there differences in neural input to the kidneys which are causative? Differences in renal insulin/insulin-like growth factor action that enhance phosphorylation of serum and glucocorticoid inducible kinase? Differences in with-no-lysine kinase signaling in renal tubular intercalated cells? These might allow constitutive dephosphorylation (and thus the possibility of activation) of MR phosphorylated on serine 843, normally requiring angiotensin as a stimulus, as elegantly recently demonstrated by Lifton and colleagues.5 If this were the case, the dephosphorylated MR in intercalated cells (unprotected by 11βHSD2) would be constitutively activated by cortisol,6 leading to MR-dependent but aldosterone independent sodium retention, as the substrate for the apparently exaggerated effect of fludrocortisone on weight and BP in blacks.

If the mechanisms underlying the differences remain in the realm of conjecture, the implications do not. Variations in sensitivity to aldosterone may be most graphically illustrated between white and black: there is evidence, albeit indirect, for a similar range of sensitivity within populations. When epelorenone as monotherapy was dose-titrated in 397 essential hypertensives, considerable variation in the dose required to reduce DBP <90 mm Hg was found.7 After 50 mg/d for 4 weeks, >40% attained goal DBP, with the nonresponders then receiving 100 mg/daily from weeks 5 to 8. A third responded with substantial BP falls, to or beyond goal DBP; the remainder received 200 mg/d from weeks 8 to 12. By week 12 half of this group had responded, with the other half (20% of the total) essentially totally unresponsive in terms of BP at any dose. Responder versus nonresponder status correlated with none of the variables measured (including urinary [K+]1 except one: at each dose, subjects with lower starting DBP were unsurprisingly slightly more likely to attain goal DBP <90 mm Hg. One of the inferences of the study is that there is at least a 4-fold, and possibly a much higher, variation in individual sensitivity (of BP) to MR antagonism, which might reasonably interpreted as reflecting a similar variance in sensitivity to MR agonists.

The authors of the Tu et al1 article note “the present findings…raise the question of what constitutes a normal aldosterone level in blacks.” This is demonstrably the case from their data, but the question needs to be raised more generally. So-called normal limits for aldosterone vary widely (4–21 ng/dL at the Mayo clinic, 3–31 ng/dL in Ancona, etc.). This 5- to 10-fold variation is not only wide but does not take into account variations in sensitivity, at the levels shown between black and white by Tu et al1 or suggested by the finding of Levy et al.2 Where this lacuna in our thinking, that it is only the plasma concentration that matters, really bites in is for the diagnosis of primary aldosteronism. Where the diagnosis of primary aldosteronism is important is in the availability of targeted therapy and the demonstration3 that patients with primary aldosteronism have much higher levels of cardiovascular risk than age-, sex-, and BP-matched essential hypertensives.

Primary aldosteronism on our current criteria and with current cut-offs represents 1% of all hypertension on strict criteria and ≈10% when they are marginally more relaxed. There are multiple recent studies suggesting that the prevalence of some degree of autonomous aldosterone secretion (so defined as not to encroach on the accepted 5%–10% figure for primary aldosteronism) may be involved in ≈30% of hypertension. Some consolation might be that the present criteria pick up the more florid cases (low hanging fruit) on the basis of aldosterone:renin ratio and measurement of PAC. Against this is that the present normal levels do not take sensitivity to aldosterone into account; this is particularly disadvantages to blacks, who are sodium hyper-replete. It is a truism that the adverse cardiovascular effects of aldosterone are only seen when levels are inappropriate for salt status; the high levels in chronic sodium deficiency, well above even the expansive current normal range, are homeostatic and not deleterious.

Low renin hypertension is a description, not a diagnosis, and has been around for half a century. In a recent study from Israel,9 24 patients with primary aldosteronism were compared with 24 (of a total of 39 seen sequentially in the clinic) subjects with a positive aldosterone-to-renin ratio but low renin hypertension, on the basis of PAC below the accepted upper limit. All patients were put on low-dose MR antagonists and followed up for 1 to 3 years. The effects were spectacular improvements in BP and left ventricular mass index, the extent of which was indistinguishable between the 2 groups. Primary aldosteronism, as currently defined, occurs in 12% to 20% of subjects with resistant hypertension, in turn defined as elevated BP, despite 3 antihypertensives including a conventional diuretic: extent of the lowering of BP by the addition of an MR antagonist is again indistinguishable across the groups, whether aldosterone is above the accepted normal range. Finally, in studies from Greece10 on referred hypertensive patients subjected to a dexamethasone-enhanced fludrocortisone/saline suppression test, 30% showed PAC values above the 97.5% figure for normotensives undergoing such a test in parallel.

Although what determines variations in sensitivity to aldosterone between individuals, and in particular between blacks and whites, is currently unclear, what is clear is that sensitivity as well as plasma level needs to be factored into judgment about what are appropriate or inappropriate levels of aldosterone. The evidence for sensitivity variation to date has come primarily by extrapolation from what are essentially default
studies using MR antagonists. The study by Tu et al takes the case a crucial step forward, by a direct demonstration of differences in sensitivity. They have made a convincing case for reconsidering “…the question of what constitutes a normal aldosterone level in blacks, and at what level it is too high, especially for the level of PRA and thus amenable to a treatment that mitigated aldosterone’s action.” In so doing they have reminded us that endocrine physiology embraces both signal and receptor; as noted above, in chronic sodium deficiency, high levels of aldosterone have no deleterious cardiovascular effects (of the sort seen in primary aldosteronism), where the renal tubule is highly responsive but nonepithelial MR unscathed. Pathophysiology is no different, in needing to embrace more than just level of signal; we thus need to recalibrate our diagnosis of primary aldosteronism, taking variation in sensitivity into account.

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