Hypertension in Blacks

Individualized Therapy Based on Renin/Aldosterone Phenotyping

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The prevalence of hypertension in blacks is higher than in other groups. The following is quoted from the 2015 statistical report of the American Heart Association[1]: "In 2009 to 2012, the age-adjusted prevalence of hypertension was 44.9% and 46.1% among non-Hispanic black men and women, respectively; 32.9% and 30.1% among non-Hispanic white men and women, respectively; and 29.6% and 29.9% among Hispanic men and women, respectively."

In the national REGARDS cohort (Reasons for Geographic and Racial Differences in Stroke)[2], among 27 744 participants followed up for 4.4 years (2003–2010), the overall age- and sex-adjusted black/white incidence rate ratio for ischemic stroke was 1.51, but for ages 45 to 54 years, it was 4.02, whereas for those ≥85 years of age, it was 0.86. This suggests that those who survived to 85 years of age did not have resistant hypertension.

Among blacks, compared with whites, the relative risk of intracranial atherosclerotic stroke was 5.85; of extracranial atherosclerotic stroke, 3.18; of lacunar stroke, 3.09; and of cardioembolic stroke, 1.58.[3] Similarly, Markus et al[4] reported that in South London, United Kingdom, the relative risk of stroke because of small vessel disease in black patients was 2.94 (95% confidence interval, 1.97–4.39; $P<0.001$) after adjustment for age, sex, risk factors, and social class. In the Northern Manhattan study, >20 years of age, the age-adjusted relative risk of intracerebral hemorrhage among blacks compared with white patients was 2.4 for men and 3.2 for women.[5] In the Northern Kentucky study, "The greatest excess risk of ICH in blacks compared with whites was found among young to middle-aged (35 to 54 years) persons with brain stem (RR, 9.8; 95% CI, 4.2 to 23.0) and deep cerebral (RR, 4.5; 95% CI, 3.0 to 6.8) hemorrhage."[6] Strokes due to small vessel disease (true lacunar infarctions in the vascular centrencephalon and intracerebral hemorrhages) are almost entirely because of high blood pressure.[7]

Strokes due to hypertensive small vessel disease can be virtually eliminated with control of hypertension. In London, Ontario, strokes were reduced by half between 1978 and 1983,[8] by a program mounted by the Department of Family Medicine[9] in cooperation with a hypertension clinic in which therapy was based on stimulated renin testing.[10] The strokes that were eliminated were mostly those due to small vessel disease (lacunar infarctions and intracerebral hemorrhages).[8] In the NASCET (North American Carotid Endarterectomy Trial), intracranial hemorrhages were reduced to 0.5% of strokes by insisting that investigators intensify medical therapy if blood pressure (BP) at any clinic visit was above the target.[11] That approach overcame therapeutic inertia, an important cause of uncontrolled hypertension. However, what seems to be more difficult to overcome is diagnostic inertia; failure to investigate the underlying cause of hypertension.[12,13] It is diagnostic inertia that we seek to diminish by this review.

In the REGARDS study, between the 45 and 64 years of age (an age group in which blacks are at 2×–3× the risk of stroke as whites), ≈40% of the excess stroke risk in blacks was attributable to traditional stroke risk factors, with levels of systolic BP accounting for approximately one half of this impact.[2] "For each 10 mm Hg increase in levels of SBP, the increased stroke risk in whites is ≈8%; however, a similar 10 mm Hg increase in SBP in African Americans is associated with a 24% increase in stroke risk, an impact 3 times greater than in whites."

Furthermore, black patients were more likely to be aware they were hypertensive, more likely to be treated for hypertension, more likely to treated more intensively, but less likely to have their BP controlled.[2] Hypertension was also more severe in blacks; at baseline, ≈40% of blacks but only 25% of whites had systolic pressures >160 mm Hg.[2]

Hypotheses seeking to explain the excess of hypertension in blacks have tended to emphasize psychological stress and socioeconomic factors.[14] In this review, we focus on biological reasons for the disparity in hypertension and stroke, because they are within the purview of physicians and provide at least a partial solution to this disparity that can be implemented immediately.

Black Hypertensives Tend to Retain Salt and Water

The kidney is crucial for the maintenance of sodium (Na) and water balance. It filters ≈25 000 mmol of sodium per day and excretes <1% of the filtered load, as illustrated in the Figure. The daily consumption of sodium ranges from ≈20 to 40 mmol in typical hunter-gatherer environments to ≈300 mmol per day in modern societies.[15] Any defect in sodium reabsorption, as exemplified by the Barter and Gitelman syndromes, where there is failure to adequately reabsorb sodium in the thick ascending loop of Henle and distal convoluted tubules, has catastrophic results for an affected individual. It results in salt wasting, hypotension, massive activation of the renin-angiotensin-aldosterone system, and severe hypokalemia.

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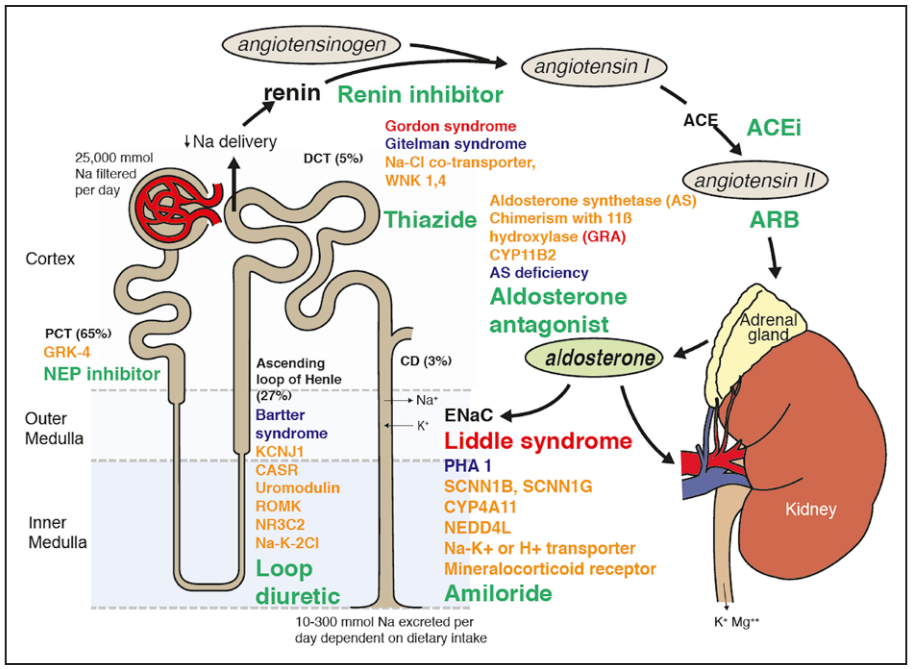

Figure. Schematic representation of sodium handling by the kidney, syndromes causing hypotension and hypertension, genetic factors influencing sodium reabsorption, and potential targeted therapeutic options. Red denotes syndromes causing sodium retention and hypertension; blue denotes syndromes causing sodium wasting and hypotension, orange denotes genes influencing sodium reabsorption; and green denotes specific antihypertensive drug classes indicated. In brackets, approximate sodium reabsorption in segments of renal tubules. ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; AS, aldosterone synthase; CASR, calcium sensing receptor; CT, collecting duct; CYP4A11, cytochrome P450, family 4, subfamily A, member 11; DCT, distal convoluted tubule; ENaC, epithelial sodium channel; GRA, glucocorticoid remedial aldosteronism; GRK4, G protein-coupled receptor kinase 4; KCNJ1, potassium voltage-gated channel, subfamily J, member 1; NEDD4L, neural precursor cell expressed developmentally downregulated 4, E3 ubiquitin protein ligase; NEP, neutral endopeptidase; NR3C2, nuclear receptor subfamily 3, group C, member 2; PCT, proximal convoluted tubule; PHA, pseudohyperaldosteronism; ROMK, potassium inwardly-rectifying channel; SCNNB1, sodium channel epithelial 1 beta subunit; SCNN1G, sodium channel epithelial 1 gamma subunit; and WNK 1,4, lysine deficient protein kinase 1, 4. The figure was prepared by Michael Wyeth of Imago-Visual, Cape Town, South Africa.

For people living in a typical hunter-gatherer population, sodium is scarce, and hypertension is rare.[15] They are in a critical sodium balance, and any minor defect in sodium reabsorption may result in loss of circulatory homeostasis, potentially resulting in environmental pressure to select genes that retain sodium more actively. This may have been an important factor in the survival of blacks during their passage from Africa to America on the slave ships.[16]

There are well-known hereditary disorders exemplified by the Liddle syndrome, where there is overactivity of the renal tubular epithelial sodium channel (ENaC) arising from activating mutations in the β- and γ-chains (*SCNN1B* and *SCNN1G*, respectively). This results in hypertension because of sodium retention, with potassium excretion and low plasma levels of both renin and aldosterone. As water follows sodium, this mechanism is also responsible for greater water preservation.

Sodium reabsorption by the kidney is illustrated in the Figure. Location and percentage of sodium reabsorption and hormonal and genetic factors that influence sodium reabsorption or excretion are shown, as well as potential for therapeutic intervention in hypertension.[17,18] Overactivity of ENaC is a key candidate for the development of hypertension because it is the final regulator of sodium balance in the kidney and accounts for ≈3% of sodium reabsorption in exchange for potassium. This occurs either through increased activity caused by mutations affecting its function or stimulation via aldosterone. Activity of ENaC is determined by the number of channels expressed on the cell surface. Under physiological circumstances, ENaC expression is promoted by aldosterone and internalized and degraded by NEDD4, a ubiquitin E3 ligase protein.[19] Mutations in the β- and γ-chain, or NEDD4 itself may result in limited degradation of ENaC and greater expression on the cell surface, and hence greater activity in response to aldosterone.[19]

Aldosterone stimulates the ENaC to reabsorb sodium in response to sodium depletion through activation of the renin-angiotensin-aldosterone system (Figure). Genetic mutations in aldosterone synthetase (CYP11B2 [cytochrome P450, family 11, subfamily b, member 2] or chimerism of aldosterone synthetase and 11B-hydroxylase) may result in greater synthesis of aldosterone and may protect individuals from sodium depletion especially in hot and arid environments.[17] In a recent physiological treatment of hypertension study done in 3 African countries, subjects with suppressed renin and increased aldosterone were screened for single nucleotide polymorphisms (SNPs) in aldosterone synthetase. These were found in 100% of the 14 tested.[20] Aldosterone production in response to low sodium intake acting in concert with increased expression of ENaC on the cell surface described above may enhance the ability to retain sodium by the kidney (Figure).

Black Hypertensives Are More Likely to Have a Liddle Phenotype

The hallmark of the Liddle phenotype, with overactivity of ENaC, is suppression of both renin and aldosterone. This phenotype is more common in blacks. For example, in South Africa, renin and aldosterone were significantly lower in blacks than whites in normotensive and hypertensive subjects despite comparable sodium intake,[21] indicating that this may be because of genetic factors. In another study from South Africa, sodium excretion in the kidney was found to be highly hereditable in blacks.[22]

Similarly, in the United States, normotensive blacks had significantly lower renin and aldosterone than whites.[23] However, crucially, after stimulation of the ENaC with 9-α fludrocortisone for 2 weeks, there was a significant rise in 24-hour ambulatory systolic BP, increase in body weight and natriuretic peptides only in blacks,[23] strongly suggesting increased retention of sodium and water mediated through the ENaC.

Whether these findings in normotensive blacks translate into a greater predisposition to hypertension is a crucial question and whether the failure to target aldosterone by the aldosterone antagonists spironolactone and eplerenone or the ENaC by amiloride (the specific inhibitor of ENaC) is relevant to the development of resistance to treatment with standard first-line antihypertensive drugs.

The association of SNPs in the ENaC with hypertension in blacks was first described by Baker et al[24] in London, who described an association with the T594M SNP of the β-chain of SCNN1B, but this was not confirmed by others. In South Africa, the entire β-chain was sequenced and a novel mutation, the p.Arg563Gln (or R563Q), present only in black and mixed ancestry South Africans, was found.[25] It was associated with low-renin, low-aldosterone hypertension (Liddle phenotype), hypertension in kindreds, and early severe preeclampsia. It was not seen in blacks living in West Africa. Overall, it was found in 5.9% of hypertensive patients in South African, including the Nguni-Zulu (9.1%), Sotho 6.4%, Nguni-Xhosa (6.3%), and mixed ancestry (4.1%).[26] Further studies showed that 20% of unselected San people (the original hunter-gatherers of Southern Africa living largely in arid and hot environments) had this variant, suggesting this was the origin of the mutation.[26] The San people have largely integrated with the black population in Southern Africa. In the San, it was not associated with hypertension, presumably because of hot arid conditions and because sodium intake was 50% lower than hypertensives living in Cape Town. Furthermore, in patients with resistant hypertension and the p.Arg563Gln SNP, amiloride, a specific inhibitor of ENaC, resulted in a 36/17 mm Hg reduction in BP. In China, the prevalence of genetically confirmed Liddle syndrome was present in 1.72% of subjects <30 years of age with low-renin hypertension.[27] In the United States, Tapolyai et al[28] found the Liddle phenotype (low renin/low aldosterone) in 6% of patients attending a Veteran's Administration hospital in LA (the investigators were not able to tell J.D.S. if those with the Liddle phenotype were more likely to be black).

SNPs in the *NEDD4* gene that regulate the degradation of the ENaC have also been linked to increased BP, as well as adverse cardiovascular outcomes, and are also likely to respond to amiloride.[29,30] Another variant (rs3890011) of CYP4A11 (cytochrome P450, family 4, subfamily A, member 11) is associated with hypertension in humans, which results from increased sodium reabsorption because of constitutive activation of the channel (ENaC) mediated by a decrease in epoxygenase activity and renal synthesis of epoxyeicosatrienoic acids and is responsive to amiloride.[31]

In a recent hypertension study done in 3 African countries, several candidate genes for the Liddle phenotype were sequenced in 14 patients. "There were 4 non-synonymous variants (NSV) of GRK4 (R65L, A116T, A142V, V486A): at least one was found in all patients; 3 were previously described and associated with hypertension. There were 3 NSV of SCNN1B (R206Q, G442V, and R563Q); 2 previously described and 1 associated with hypertension. NPPA (natriuretic peptide precursor A) was found to have 1 NSV (V32M), not previously described, and NEDD4L did not have any variants. UMOD had 3 NSV: D25G, L180V, and T585I."[20]

Black Hypertensives Are More Likely to Have Primary Aldosteronism

In addition to having more renal tubular absorption of salt and water related to overactivity of ENaC, as discussed above, it is also likely that there is more primary aldosteronism because of bilateral adrenocortical hyperplasia among black patients.[10,32–36] This was reviewed in 2017.[37] The recent American Heart Association/American College of Cardiology recommendations[38] on aldosterone/renin ratio are focused on identifying patients for adrenalectomy and require withdrawal of aldosterone antagonists for 4 to 6 weeks for interpretation of the results. Here, we are emphasizing phenotyping by renin and aldosterone for medical therapy, and as discussed above, plasma renin levels obtained in a stimulated condition are more informative than unstimulated plasma renin levels. Because the primary aldosteronism is usually because of bilateral hyperplasia, it is usually best treated medically; only a small percentage require adrenalectomy, and in very severe cases a complete adrenalectomy on 1 side with a partial adrenalectomy (attempting to spare some normal tissue) may be required.[10] In our African study,[20] all the patients with primary aldosteronism phenotype had variants of aldosterone synthase. Unfortunately, we did not have sufficient funds to sequence candidate genes for the Liddle phenotype in those patients; it seems likely that some/many black patients have variants of genes that predispose to both the primary aldosteronism and the Liddle phenotype. The coexistence of variants causing both Liddle phenotype and primary aldosteronism may complicate the diagnosis of biochemical primary aldosteronism. This should be investigated further. Patients with a high aldosterone/renin ratio respond to amiloride in a similar manner to low-dose spironolactone,[39] but aldosterone antagonists would be preferred if feasible (ie, if men who have gynecomastia from spironolactone can afford to pay for eplerenone) because of the effects of aldosterone on the myocardium and the arteries independent of BP.[40,41]

Black Patients Respond Preferentially to Diuretics

Greater salt and water retention in black patients probably accounts for the differences in response to antihypertensive drug classes in 3 large trials conducted on different continents.

In the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) in the United States, in which 40% of participants were black, diuretic was the most successful drug class.[42] In contrast, in the ASCOTBPLA (Anglo-Scandinavian Cardiac Outcomes Trial)[43] in which only 2.4% of participants had African ancestors,[44] amlopidine to which perindopril was added was more effective than atenolol to which thiazide diuretic was added. In the second ANBP2 study (Australian National Blood Pressure),[45] in which <2% of participants were black,[44] angiotensin-converting enzyme inhibitors were more effective than diuretics.

African Diaspora Hypothesis

It has been hypothesized that blacks have more hypertension because of natural selection for survival conferred by genetic causes of salt and water retention, during the severe conditions of heat and privation between decks on slave ships bringing slaves from Africa to the Caribbean and to the United States. Mortality rate was high and commonly because of vomiting from seasickness, diarrhea, and profuse sweating.[46] That natural selection played a part is supported by evidence of genetic differences between African and black populations[47] and by a higher prevalence of hypertension among blacks versus African residents.[46] A recent study from the National Health and Nutrition survey reported that 42.8% of US-born blacks but only 27.4% of foreign-born blacks had hypertension.[14]

Physiologically Individualized Therapy Based on Plasma Renin and Aldosterone

Laragh et al[48] was perhaps the first to propose that therapy for hypertension could be refined by measurement of plasma renin activity. He focused on volume hypertension in patients with low plasma renin activity. Spence[10] reported in 1999 on 20 years' experience of renin-based therapy in a hypertension clinic, noting that, particularly among patients with severe resistant hypertension, stimulated plasma renin activity was extremely helpful, particularly by identifying patients with primary aldosteronism and renovascular hypertension for individualized therapy. Reasons why this approach was not widely adopted probably include that it is not helpful in patients with easily controlled hypertension and that unstimulated plasma renin levels are not informative. Sodium intake is so high in the United States that renin is suppressed in many/most patients. To reveal suppression of plasma renin activity independent of sodium intake, it is necessary to measure plasma renin in a stimulated condition.[49]

In 2006, Spence[44] suggested that physiologically individualized therapy based on phenotyping with plasma renin and aldosterone had the potential to eliminate or at least markedly diminish the racial disparities in hypertension and stroke in the United States. Some guidelines recommend differential treatment of hypertension based on race[50]; Bonham et al[51] suggested in 2016 that genotyping for personalized medicine may be helpful in moving beyond race. However, there are many genetic variants that contribute to hypertension, and specific therapies are not known for many of them.[52] The Figure lists some of them. Furthermore, we found in our African study that most patients with the Liddle phenotype had variants of several different genes affecting ENaC function.[20] Individualized therapy for hypertension may, therefore, be better done by phenotyping patients with stimulated plasma renin and aldosterone to identify the physiology of hypertension in the individual patient.

Table. Physiologically Individualized Therapy* Based on Renin/Aldosterone Profile

Phenotyping and Primary Medical Therapy	Primary Hyperaldosteronism	Liddle Syndrome and Variants (Mutations Affecting ENaC† or its Function‡)	Renal/ Renovascular
Renin	Low§	Low	High
Aldosterone	High§	Low	High
Primary treatment	Aldosterone antagonist (spironolactone or eplerenone)	Amiloride	Angiotensin receptor blocker or renin inhibitor‖
	Amiloride for men where eplerenone is not available (rarely surgery)		(Rarely revascularization)

*It should be stressed that this approach is suitable for tailoring medical therapy in resistant hypertensives; further investigation would be required to justify adrenalectomy or renal revascularization.

†ENaC denotes renal tubular epithelial sodium channel, SCNN1B.

‡GRK(G protein-coupled receptor kinase), NEDD4L (neural precursor cell expressed developmentally downregulated 4), CYP4A11 (cytochrome P450), NPPA (natriuretic peptide precursor A), and UMOD (uromodullin).

§Levels of plasma renin and aldosterone must be interpreted in the light of the medication the patient is taking at the time of sampling. In a patient taking an ACE (angiotensin-converting enzyme) blocker or angiotensin receptor blocker (which would elevate renin and lower aldosterone), a plasma renin that is in the low normal range for that laboratory, with a plasma aldosterone in the high normal range, probably represents primary hyperaldosteronism for the purposes of adjusting medical therapy.

‖ACE inhibitors are less effective because of aldosterone escape via non-ACE pathways, such as chymase and cathepsin; renin inhibitors are seldom used.

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A randomized clinical trial in the United States by Egan et al[53] in patients with resistant hypertension gave some indication that renin-based therapy for hypertension was better than usual care (UC). Although they did not demonstrate a significant improvement in BP control, they found a trend to improved BP control and a greater reduction of medication required by patients with low-renin hypertension. However, there are 2 main groups of low-renin hypertensives: those with a primary aldosteronism phenotype (low renin/high aldosterone), for whom the best therapy is aldosterone antagonists and those with a Liddle phenotype (low renin/low aldosterone), for whom the specific therapy is amiloride. Patients with a renal phenotype (high renin with secondary hyperaldosteronism) respond best to angiotensin receptor blockers or renin inhibitors. Occasionally, patients with true renovascular hypertension may require renal revascularization.[54,55] Renovascular hypertension is more common in patients with carotid stenosis.[56] It is, therefore, more informative in individualizing therapy to measure both stimulated plasma renin and

aldosterone. An algorithm for this approach is shown in the Table. In brief, plasma renin (preferably plasma renin activity if available) and aldosterone are measured in a stimulated condition. Laragh and colleagues[58] used captopril for this purpose, whereas Dawson and colleagues[49] recommended furosemide. Spence[10] used furosemide ≈0.5 mg/kg given 4 hours before blood sampling for local patients or intravenously 30 minutes before blood sampling for patients coming from far away (to avoid inconvenience from polyuria during the drive to clinic). For patients already taking drugs that stimulate renin (diuretic, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker), this step is not necessary. Other investigations (electrolytes, creatinine, etc) would be as routine for hypertension. The results must be interpreted in the light of the medication being taken at the time of blood sampling. For example, angiotensin receptor blockers raise renin and lower aldosterone. Therefore, a patient taking an angiotensin receptor blocker, who has a low normal renin and a high normal aldosterone level, would be regarded as having primary aldosteronism for the purpose of adjusting medication; further investigations would be regarded if adrenalectomy were a consideration.

Evidence supporting this approach is now available from a clinical trial in hypertension clinics in Nigeria, Kenya, and South Africa.[57] Patients whose BP was not controlled to <140 systolic or <90 diastolic were allocated to usual care (UC) versus physiologically individualized therapy (PhysRx). This approach was not effective in the Kenyan clinic, where there were fewer visits and fewer medications prescribed, amiloride was not available, and there may have been problems with affordability of medications, as well as cultural reasons/health beliefs for noncompliance.

In the overall study, control of both systolic and diastolic pressures was obtained in 11.1% of UC versus 50.0% of PhysRx (P<0.0001). Systolic control was achieved in 13.9% of UC versus 60.3% of PhysRx (P<0.0001); diastolic control in 36.1% of UC versus 67.2% of PhysRx (P=0.003). When only the sites in Nigeria and South Africa were considered, systolic control was obtained with PhysRx in 15% of UC versus 78.6% with PhysRx (P<0.0001), diastolic control in 45% versus 71.4% (P=0.04), and control of both in 15% versus 66.7% (P<0.0001). At the Nigerian site, where patients were randomized and conditions were more similar to those in North America, systolic control was obtained in 15% of UC versus 85% of PhysRx (P<0.0001), diastolic control in 45% versus 75% (P=0.11), and control of both systolic and diastolic pressures in 15% versus 75% (P<0.0001) even though the renal function was worse at that site.

The biggest difference in medication change during the study was with amiloride; at the end of the study, amiloride was being taken by 19% of PhysRx patients versus only 2.8% of UC (P=0.02). It is notable that amiloride is seldom prescribed by physicians following guidelines. Indeed, neither Liddle syndrome nor amiloride is even mentioned in the Eighth Joint National Committee guideline[50]; in the 2017 guideline,[38] amiloride is mentioned only as a potassium-sparing diuretic, and Liddle syndrome is not mentioned in the executive summary. In the full guideline, Liddle syndrome is mentioned only to say it is rare.

This approach is also useful in treatment of potassium depletion, by identifying the cause. Potassium supplements are not effective in restoring intracellular potassium unless given with magnesium,[59] whereas amiloride is both magnesium- and potassium-sparing,[60] and aldosterone antagonists also prevent renal excretion of both magnesium and potassium.[49]

Conclusions

Black patients of African origin have more severe and resistant hypertension, often because of genetically determined predisposition to salt and water retention, with suppressed plasma renin activity. A Liddle phenotype (low renin/low aldosterone because of overactivity of ENaC) is much more common than most physicians appreciate. To identify what is the best medical therapy for an individual patient, it is important to determine the physiological drivers of the hypertension. If the patient has a Liddle phenotype, amiloride is the specific therapy; for a primary aldosteronism phenotype, aldosterone antagonists are the best medical therapy; adrenalectomy is rarely indicated. For a renal phenotype, antagonists of the renin/angiotensin system are the best medical therapy; occasional patients may require renal revascularization. This approach should be tested in randomized trials in the United States and elsewhere, not only in black patients but also in patients with resistant hypertension of any racial/ethnic origin.

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Disclosures

None.

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