Evolution of Diagnostic Criteria for Primary Aldosteronism: Why Is It More Common in "Drug-Resistant" Hypertension Today?

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The recent "epidemic" of primary aldosteronism reported in the literature is most likely related to the widespread acceptance that with easy access to accurate measurements of renin and aldosterone, it is no longer necessary to wait until hypokalemia has become profound before embarking on diagnostic testing to attempt to ferret out this most common cause of "essential" hypertension. This is especially true for those who are now classified as "drug resistant" using today's popular drugs, which are particularly ineffective in lowering blood pressure in primary aldosteronism and its variants. Understanding the physiologic consequences of a slowly increasing aldosterone production by autonomous cells will help both the family practitioner and the specialist understand the role of the aldosterone renin ratio (ARR) in the care of the hypertensive patient. In addition, the increasing number of specific genetic mutations that drive sodium retention and lead to low levels of renin activity and familial hypertension must be incorporated into the routine evaluation and care of hypertensive patients and their families.

Introduction

The goal of this review is to place the surge of reports of a high prevalence of "primary aldosteronism," especially in those with "drug resistant hypertension," into the context of our understanding of the physiologic evolution of the syndromes of primary aldosteronism (PA). Understanding the time course of the physiologic disturbances as the body's blood pressure (BP) control systems are assaulted by a gradually increasing exposure to a pathologic (classically autonomous) source of aldosterone is crucial to the clinical application of the new diagnostic criteria for PA using the aldosterone/renin ratio (ARR). As aldosterone production increases, the ensuing physiologic changes evolve into the criteria classically used to diagnose PA: hypertension, hypokalemia, suppressed plasma renin (after sodium depletion), and increased aldosterone production reflected by increased plasma and/or urinary aldosterone excretion that cannot be suppressed normally with saline infusion, high dietary sodium intake, or administration of exogenous mineralocorticoid. Of course, the final proof of the diagnosis rests on reversal of the endocrine manifestations of excess aldosterone production by aldosterone-blocking drugs, removal of the offending tissue, or suppression of other stimuli to excess aldosterone production. New advances in the genetics of sodium metabolism by the kidney have shed light on the causes of high BP that runs in families and causes changes in the ARR.

The Historical Evolution of Primary Aldosteronism.

It has been 50 years since Dr. Jerome W. Conn reported the first case of PA [1••].

> In April, 1954, a 34-year-old female patient with a bizarre constellation of clinical and laboratory manifestations was presented to me on ward rounds. They included periodic paralysis, intermittent muscular weakness, episodic tetanic manifestations, polydipsia and nocturnal polyuria, headache, hypertension, positive Chvostek and Trousseau signs, hypokalemia (1.5 mM/L), hypernatremia (151 mM/L), alkalosis, alkaline urine with a mild proteinuria…It required 8 months of continuous metabolic study of that patient to put all the multiple manifestations satisfactorily into the syndrome that I then called primary aldosteronism [2].

Surgical extirpation of a 4-cm right adrenal adenoma reversed all of the clinical and laboratory abnormalities. Dr. Conn's group was the first to note that plasma renin activity (PRA) was very low in PA, whereas it was elevated

in patients with renal artery stenosis, the classic cause of secondary aldosteronism. After 10 years of careful clinical investigation of many more patients, progressively smaller tumors were removed to cure the hypertension, and it became evident that hypokalemia was not a sine qua non for PA. Dr. Conn then suggested that as many as 20% of patients with "essential hypertension" and low plasma renin activity had normokalemia PA [3,4], and the subtle disturbances of glucose metabolism, seen in many patients with hypertension (the metabolic syndrome), could be related to increased aldosterone production.

In 1966, the first case of familial aldosteronism associated with adrenal hyperplasia and reversed by dexamethasone administration was reported in a father and son in Canada [5]. The first normokalemic family with this syndrome was reported in 1977 by the Indiana group [6]. This syndrome is now called gluocorticoid remedial aldosteronism (GRA), and a series of elegant family and genetic investigations by Lifton *et al.* [7] culminated in identifying the first specific genetic mutation known to cause human hypertension.

In 1975, after spending much of my early career trying to prove Dr. Conn wrong, I concluded that he was likely correct [8]. I advanced the suggestion, which he labeled the "Grim hypothesis": most patients with what was then called "low-renin essential hypertension" (LREH) represented a forme fruste or early stage of classic PA. Recent research suggests that this hypothesis is still viable and helps to explain the "epidemic" of PA now being reported around the world, especially in those with drug-resistant hypertension [9]. The recent report from Framingham [10••], and the accompanying comments by Dluhy and Williams [11] that serum aldosterone is a major predictor of high BP in normotensive persons mandates that we rethink the relative contribution of the aldosterone component of the renin-angiotensin-aldosterone system (RAAS) in the pathogenesis of the increase in BP with age, which we call "essential hypertension."

It now seems likely that the physiologic effects of "excess" aldosterone over time leads to the rise in BP with age, and it is the rise in aldosterone-induced sodium retention that is suppressing the renin. Therefore, it is important to review the basic physiology of the control of aldosterone, renin, and BP in humans to fit this new information into earlier conjectures about the role of aldosterone in essential hypertension. It is of great interest that the circulating level of renin has almost always been reported to be inversely related to BP in population studies [12]—that is, hypertensives tend to have lower PRAs than normotensives, especially in older populations. It has generally been suggested that it is the rise in pressure from some other causes that leads to baroreceptor suppression of renin as BP rises with age. It now seems likely that it is abnormal aldosterone production that is the culprit.

Physiologic Evolution of Primary Aldosteronism

The basic premise of the hypothesis is that big tumors come from small tumors and a corollary is that macronodular (*ie*, grossly visible) hyperplasia arises from micronodular (*ie*, microscopic) hyperplasia.

Physiologic effects of giving exogenous aldosterone to a normotensive person

Figure 1 depicts the effects of giving a normal person a daily injection of aldosterone that is equal to only half of the normal aldosterone production. On the control day (*C*), the 24-hour urinary excretion of aldosterone is 8 μg/d. At baseline, the extracellular fluid volume (ECFV) and plasma renin activity are at their normal levels. On day 1, the renal tubules (and other tissues) will "see" 50% more aldosterone (the sum of the 8 μg endogenous production plus the 4 g injected) than on the control day. This results in sodium retention and an increase in ECFV, which suppresses renin production. Because the dominant regulator of aldosterone production, angiotensin II (Ang II), is controlled by the level of renin in the blood, the major drive to aldosterone production decreases, and the endogenous adrenal tissue production of aldosterone is quickly suppressed [13•]. From day 2 to day 6, the contribution of the endogenous aldosterone progressively decreases until, by day 6, the total aldosterone level (endogenous and exogenous) has returned "nearly" to normal. This sequence of events—that is, an exogenous source of a hormone resulting in suppression of endogenous hormone production—is a general principle of physiology.

The circumstances present on day 6 should be the following.

1. Total aldosterone excretion would be slightly above normal but only 50% is now coming from the normal adrenal glands.
2. ECFV must be above the control value to maintain renin suppression.
3. Suppression of renin (which is the trophic hormone that has become suppressed) must be maintained to decrease the endogenous aldosterone production. The ARR would also be increased above baseline for this person. If we tried to suppress this person's aldosterone production, he would likely suppress only to the 4 μg/d, given as exogenous aldosterone. If aldosterone production had been found to be suppressed in this person before the exogenous aldosterone was administered, a drop to lower levels would be expected.

What are the long-term consequences of this expanded ECFV? The work of Guyton *et al.* [14••] has shown that an expansion of ECFV results in increased intracellular fluid volume, increased mean systemic filling pressure, increased return of the blood to the heart, increased cardiac output, and increased BP.

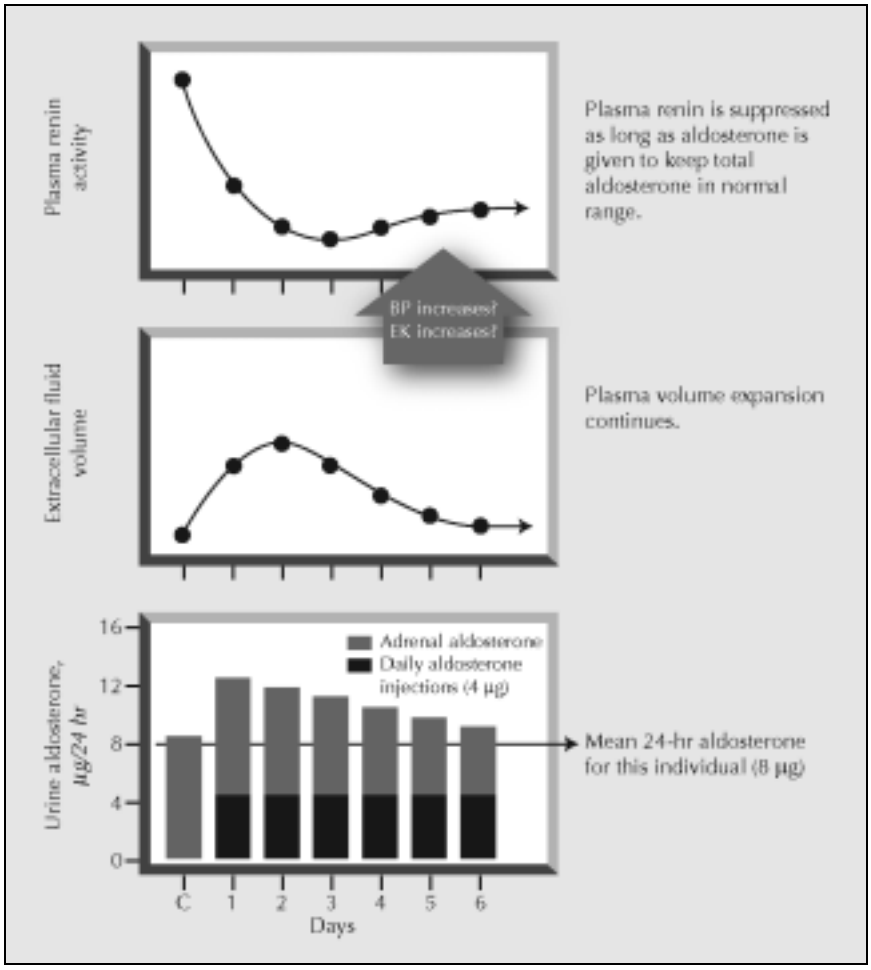

Figure 1. Hypothetical physiologic changes induced by an autonomous (exogenous) source of aldosterone that is equal to half of this subject's usual production.

This increased pressure promotes natriuresis to excrete the increased sodium retained via pressure natriuresis. If the volume effects of the increase in sodium intake cannot be compensated by the pressure natriuresis, the high cardiac output–driven, overperfusion of the peripheral vascular beds activates endogenous mechanisms of vasoconstriction (autoregulation) to keep blood flow in the regulated range. BP will rise until sodium homeostasis is restored or the heart fails. Indeed, Hall *et al.* [15•] have shown that for the kidney to escape from the sodium-retaining effects of excess aldosterone, the renal perfusion pressure must rise. Therefore, it seems reasonable to suggest that a small rise in pressure is part and parcel of the "escape" from this abnormal source of aldosterone.

The physiology of the evolution of primary aldosteronism due to an adenoma

Figure 2 applies the concepts developed in Figure 1 to depict the likely evolution of PA due to an adrenal adenoma. Four stages in this evolution are suggested.

Stage 1: Physiologic hyperaldosteronism (low-renin normotension)
Figure 2 depicts the evolution of a tumorous source of aldosterone on this same individual's physiology. Assume that at the start of this process, a single cell begins to produce aldosterone autonomously. As the tumor cells divide, they produce more and more aldosterone. As shown in Figure 1, the "injection" of this extra aldosterone by the tumor leads to progressive sodium retention, suppression of PRA, autoregulatory vasoconstriction, and increased BP. As the tumor aldosterone–induced volume expansion occurs, the renin feedback loop is progressively suppressed to lower the amount of aldosterone produced by the normal portion of the adrenal glands. As the tumor source of aldosterone increases, methods used to suppress endogenous aldosterone production, such as high salt diet, saline infusion, or administration of exogenous mineralocorticoid, would find that the "suppressibility" of plasma and 24-hour urinary aldosterone (UALDO) excretion would become progressively smaller.

For example, Collins *et al.* [16] reported that normals, who had a baseline, 24-hour UALDO of 11 μg on a 120 mM sodium intake, decreased UALDO by 20% on 190 mM sodium intake, and by 65% at 300 mM sodium per day. In these normal subjects, the lowest suppression limit was 1.0 μg/24 hours. In patients with LREH, the mean UALDO suppressed to only 9.8 μg (range 3.8–6.2 μg), whereas no patient with PA reduced their UALDO to less

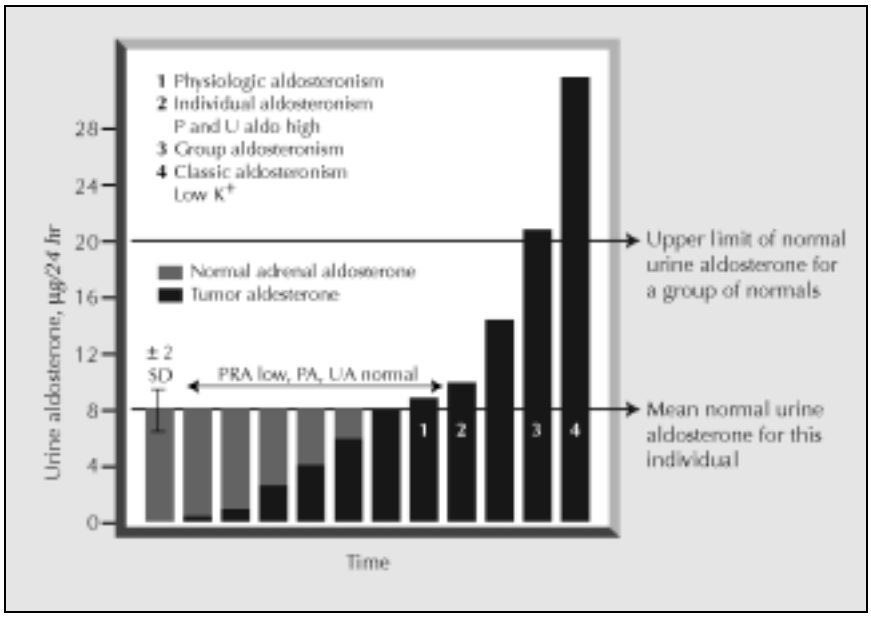

Figure 2. The evolution of aldosterone production by an adrenal tumor causing primary aldosteronism. This is a theoretic depiction of what likely happens as a small aldosterone tumor grows over time. The tumor aldosterone production is shown by the *dark, shaded area*, and the normal adrenal aldosterone production is shown by the *light, shaded area*. The upper limit of 24-hr urine aldosterone excretion is 20. This individual's pre-tumor aldosterone production is shown as 8 ±2 SD. PA—primary aldosteronism; PRA—plasma renin activity; SD—standard deviation; UA—urinary aldosterone. See text for details.

than 26 µg/24 hr. This raised the question: "If the renin-aldosterone system is not responsible for the sustained aldosterone secretion in patients with low PRA, what underlies the nonsuppressible release of aldosterone, and possibly other corticosteroids, in the patient without an adrenal adenoma?" This question is currently unanswered, as recently reviewed by Kaplan [17••].

Therefore, the earliest physiologic manifestations of this abnormal source of aldosterone would be lowered plasma renin activity, less suppressible aldosterone, and an increased ARR. Although BP likely rises as aldosterone production increases, it may not be above "normal." Again, if we had multiple BPs or 24-hr BPs, we might be able to detect a rise in pressure for this individual. I have chosen the term *physiologic hyperaldosteronism* for this stage 1 of the evolution of the syndrome.

It should be noted that with today's high salt intake, "low" renin can only be clearly defined by standardized sodium depletion, such as used in the so-called saline-lasix protocol developed by the Indiana group and tested in large numbers of normals and hypertensives [18].

Stage 2: Individual aldosteronism (low-renin essential hypertension)

Note that aldosterone excretion has been measured a number of times in the same person for several years before the onset of the tumor, and we know the mean and 2 standard deviatons (SD) of UALDO. When the aldosterone production exceeds that which this person normally produces, for example, 10 µg/24 hr, we can make the diagnosis of individual aldosteronism. Of course we do not normally have this information on the individual patient, and, therefore, this patient would be diagnosed as having low-renin essential hypertension, if the BP had risen above normal. It is important to note that, at this stage of "individual hyperaldosteronism," the urine aldosterone level is in the normal range for a group of individuals, but is clearly elevated for this individual. The ARR would increase further. It is likely that when the tumor production exceeds that normally produced by this individual, the BP and potassium excretion will increase further in an attempt to escape from the sodium-retaining effects of the now "elevated" aldosterone. Assuming the BP has risen above "normal," this person now has LREH: hypertension with low renin and normal aldosterone. The striking finding that the use of the ARR to screen for PA around the world has decreased the prevalence of hypokalemia from as high as 98% at the Mayo Clinic before the use of the ARR to only 30% suggests that the use of the ARR is diagnosing more patients in stage 2 of the disease (LREH). Adrenal pathology documents that most of these patients have what appears to be early adenomas or early hyperplasia [19,20•]. It is critical to note that the laboratory should have studied large numbers of normal subjects to be able to define what is "normal" by age, gender, and ethnicity. Few centers have done this with the ARR.

Further evidence that the "normal" levels of aldosterone are driving the hypertension in LREH [21•] comes from the demonstration that blocking aldosterone production by the adrenal steroid biosynthetic inhibitor aminoglutethimide lowered weight, BP, and aldosterone excretion rates in only 4 days, and the effects were continued for the 21 days the drug was given. The striking effect of the new aldosterone receptor blocker eplerenone in LREH also supports a key role for aldosterone in this syndrome [22], as have older studies with spironolactone.

Stage 3: Group hyperaldosteronism (normokalemic primary aldosteronism)

The tumor continues to grow, and the person enters stage 3, group hyperaldosteronism, when the 24-hr urinary aldosterone exceeds the upper limit of normal for the laboratory

(20 μg/d). The renin would be lower, the aldosterone higher, and the ARR higher than in stage 2. Aldosterone production would no longer suppress into the "normal" range, and hypokalemia might be precipitated by a low potassium intake, diuretic use, or extrarenal loss of potassium in sweat, vomit, or stool.

Stage 4: Classic hyperaldosteronism (hypokalemic primary aldosteronism).
It has been known since the earliest work of Conn [23••] and Chobanian *et al*. [24] that exogenous mineralocorticoid can cause severe hypertension and hypokalemia. As the tumor aldosterone production becomes massive, full-blown Conn's syndrome manifests as severe and drug-resistant hypertension.

Ultimately, the practitioner is presented with the myriad physiologic effects of profound hypokalemia: nocturia and polyuria from antidiuretic hormone (ADH) resistance; cramps in the hands, feet, and legs, especially with exercise; increasing fatigue; profound weakness and periodic paralysis; cardiac arrhythmias; and even cardiac arrest [25]. Many will also have diabetes due to the effect of hypokalemia to impair insulin release. Although one would hope that most patients with PA would be diagnosed before disability and life-threatening events have evolved, a website (hyperaldosteronism@yahoogroups.com) for patients with PA is regularly joined by a new person who has a dramatic story of their frustrating journey though the medical establishment before the diagnosis has finally been made. I recommend that all practitioners, including those who specialize in hypertension (and their patients with PA), visit this site for many items of interest to the management of this most common, treatable, and curable cause of hypertension.

Note that the ARR will increase progressively from stage 1 to stage 4, and the suppressibility of UALDO will progressively decrease. Rigid definitions of what is "normal" and "high" can only be determined by the study of a large group of normals adjusted for age, gender, and ethnicity, with careful control of posture, time of day, mealtime, and sodium/potassium intake. This is difficult, if not impossible, without an overnight stay on a metabolic unit. The cut-off points for "curable hyperaldosteronism" for each stage must be rigidly defined by results of adrenal vein sampling and/or the reversal of the syndrome following removal of the offending tissue [26]. Careful standardization of collection methods and pooling of results around the world will likely be needed to define standards that will be useful for the practitioner.

The possibility that patients with low-renin hypertension may have a curable form of hypertension due to abnormal aldosterone production by a very small group of adrenal cells makes efforts to localize the abnormality to one or both adrenal glands an important next step. If they are unilateral, the hypertension and hypokalemia can be cured by unilateral laparoscopic adrenalectomy, which often requires only 2 to 3 days of hospitalization. However, I currently reserve the definitive localization study (adrenal vein sampling for aldosterone and cortisol with adrenocorticotropin hormone [ACTH] stimulation [27]) for those patients whose BP cannot be controlled with multiple medications, including the aldosterone-blocking agents spironolactone or eplerenone. My "cocktail" for control of these difficult patients nearly always includes a combination of a β-blocker with a diuretic, an ACE or ARB, and with a CCB and an aldosterone-blocking agent. In many cases, once the BP is controlled with this combination of combinations, all but the aldosterone-blocking agents can be tapered, and the BP still be maintained at goal.

Why Do Patients with "Drug-resistant" Hypertension Have an Increased Prevalence for Primary Aldosteronism?

The search for the diagnosis of PA has, in the past, been reserved for those with either hypokalemia or "drug resistant" hypertension. Currently, the frequency of PA can be expected to be increased because the drugs used to treat hypertension have changed. The physiology of "drug resistant" hypertension has shifted to syndromes that have failed to be controlled by the four drugs that are known to be less effective in patients with low-renin forms of hypertension: β-blockers, ACEs, ARBs, and CCBs [28]. The decrease in the use of diuretics and/or the use of potassium-sparing combinations may have deprived the clinician of a key clue to PA—diuretic-induced hypokalemia. However, in a recent report of a high prevalence of PA in patients with drug-resistant hypertension by Nishizaka *et al*. [29••], 75% had a low serum potassium as well as an increased ARR.

Further research should be directed at understanding the primary disturbances leading to an abnormal growth pattern of adrenal cells that results in tumor formation or hyperplasia. One relatively unexplored suggestion is that psychosocial stress, which, in mice, leads to adrenal cortical hyperplasia and hypertension, could play a similar role in humans [30•].

Familial hypertension: the genetics of low-renin forms of hypertension with high or low aldosterone levels

There have been recent, major advances in the genetics of high BP that runs in families. These mutations raise BP by causing renal sodium retention and, therefore, are associated with suppression of PRA. Because genetic testing can identify subjects before they become hypertensive, the study of the earliest physiologic alterations has shed light on the suggested sequence of events in the evolution of PA.

Familial forms of primary aldosteronism: type 1 and type II

Familial aldosteronism type I

Glucocorticoid remedial aldosteronism is now known to be the result of a chimeric gene that transfers the major stimulus for aldosterone production from Ang II to ACTH [31]. Thus, suppression of ACTH with glucocorticoids suppresses the ACTH-driven aldosterone production and normalizes the BP and, in advanced cases, the hypokalemia. It is likely that careful longitudinal study of genetically affected, but initially normotensive, family members with inherited forms of aldosteronism will document the progression of this physiologic sequence of events. Indeed, Stowasser *et al.* [32] have reported that normotensive family members who test positive for GRA tend to have suppressed PRA and an increased ARR. Therefore, these normotensives with the GRA mutation appear to be in the earliest stage of hyperaldosteronism (stage 1), as described earlier. It will be of great interest to follow the evolution of the physiology in these families to see if they progress through the last three stages of PA.

Practitioners now need to consider this syndrome in every family with hypertension. The clinical clues to GRA are early strokes in males, severe hypertension, and hypokalemia. The importance of finding these families is the hope that early treatment will prevent the early strokes and the fact that, on the average, 50% of all first-degree relatives will also be affected.

Familial aldosteronism type II

This familial syndrome was first described by Gordon *et al.* [33] and is associated with adenomas or hyperplasia and is not glucocorticoid suppressible. Genetic studies are in progress. Longitudinal studies in these families would also be expected to document the hypothesized evolution of PA.

Familial hypertension but lower renin and low aldosterone

Liddle's syndrome

This familial hypokalemic hypertension with very low renin and low aldosterone, corrected by amiloride or triampterene, is now known to be due to an inherited mutation of the gene that controls the protein makeup of the renal sodium channel (ENaC), key in reabsorbing sodium in the distal tubule [34]. The mutation leads to an increase in sodium reabsorbtion, hypertension, and suppression of renin and aldosterone that is reversed by amiloride. These patients have a very low ARR. The recent study of an extended kindred by Findling *et al.* [35] reported several members with normal BP who had suppressed renin and low blood and urine aldosterone, suggesting that they were in a prehypertensive stage of the evolution of Liddle's syndrome.

Apparent mineralocorticoid excess

Apparent mineralocorticoid excess (AME) manifests with hypertension, hypokalemia, and suppression of PRA and aldosterone, and was recently reviewed in this journal [36]. The mineralocorticoid receptor can be occupied and activated not only by aldosterone but also by cortisol. Normally circulating cortisol levels are 1000-fold higher than aldosterone levels, but the renal mineralocorticoid receptor (MR) is normally protected from activation by cortisol by a high cellular level of the key enzyme, 11β-hydroxysteroid dehydrogenase (HSD11B2), which converts cortisol to cortisone. Cortisone has minimal ability to stimulate sodium retention via the MR stimulation of sodium channels. However, in AME, this gatekeeper enzyme is deficient in the renal cells, allowing cortisol access to the MR, which increases sodium retention. The sodium retention suppresses renin and aldosterone and increases BP. Again, it will be of great interest to follow the evolution of the AME syndrome. The recent report by Wilson *et al.* [37] of a patient with BP at only the 90th percentile for age and "mild" AME suggests that the earliest manifestation of this syndrome is suppressed renin and aldosterone, before overt hypertension develops.

Licorice (glycyrrhizinic acid)-induced hypertension

Daily ingestion of licorice or items that are licorice flavored (candy, chewing tobacco, and medications) can also result in severe hypertension, hypokalemia, and suppression of renin and aldosterone, as first reported by Conn *et al.* [38••]. The mechanism appears to be due to the inhibition of HSD11B2 by the acid that provides the natural licorice flavor. This allows cortisol access to the MR [39]. Careful dose titration studies should demonstrate the evolution, as described earlier, except that aldosterone would be progressively suppressed as renin is suppressed by the sodium retention.

The Renin-Angiotension-Aldosterone System in Essential Hypertension: Have We Had It Backward?

The observation that the level of PRA has never been shown to correlate with BP in population studies suggests that the major drive to increases in BP with age in humans is not the renin-angiotensin portion of the system that elevates the high BP, but rather, the key to our understanding of essential hypertension may be the primary abnormalities of aldosterone production (in conjunction with a high sodium intake). Maybe we have had it backward. In essential hypertension, perhaps it should be called the "aldosterone-renin-angiotensin system" to reflect the rank order of importance of the physiologic control systems leading to increases in BP with age in humans.

Conclusions

A primary role for aldosterone (and high salt intake) in the pathophysiology of human essential hypertension now seems clear, and may be at least as common as those forms of hypertension primarily driven by the renin-angiotensin portion of the system. The wide availability of accurate testing with the aldosterone-renin ratio for the most common disturbance of BP control, excess aldosterone production of adrenal origin, will likely lead to better BP control in many.

Determining the ARR will enable the practitioner to sort out the causes of drug-resistant or hypokalemic hypertension that is driven by inherited alterations of the renal handling of sodium. Therefore, the ARR should be assessed in all patients with drug-resistant or familial hypertension, which will, hopefully, lead to more specific and successful treatment of many patients and their families.

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