Is Altered Adrenal Steroid Biosynthesis a Key Intermediate Phenotype in Hypertension?

John M.C. Connell, Robert Fraser, Scott MacKenzie, Eleanor Davies

Abstract—Approximately 10% of patients with hypertension have a high ratio of aldosterone to renin, but the reason for this and the relationships among low-renin essential hypertension, elevation of the ratio, and true primary aldosteronism are unclear. We have previously reported that a polymorphism of the gene (C-to-T conversion at position −344) encoding aldosterone synthase is associated with hypertension, particularly in patients with a high ratio. However, the most consistent association with this variant is a relative impairment of adrenal 11β-hydroxylation. In this review, we propose that altered conversion of deoxycortisol to cortisol leads to a subtle, chronic increase in adrenocorticotropin drive to the adrenal cortex, with eventual development of hyperplasia. In combination with other genetic or environmental factors (such as dietary sodium intake), we suggest that this might be responsible for the long-term development of a resetting of the aldosterone response to angiotensin II, giving rise to the phenotype of hypertension with a raised ratio. In some subjects, this may progress further to true primary aldosteronism with a dominant adrenal nodule. Thus, there may be a genetically influenced continuum from hypertension with a normal ratio, through hypertension with a raised ratio, and primary aldosteronism. (Hypertension. 2003;41:993-999.)

Key Words: hypertension, mineralocorticoid ■ adrenal gland ■ aldosterone ■ adrenocorticotropin hormone

Despite many years of research, the pathophysiology of essential hypertension remains uncertain, and it seems likely that no single cause exists. This may best be appreciated by considering the lessons from rodent models of hypertension. Here, selective inbreeding has generated strains that develop high blood pressure through a range of distinct mechanisms. For example, the role of adducin in the Milan hypertensive rat contrasts with the involvement of corticosteroids in the Dahl salt-sensitive strain; in each instance, distinct genetic loci can be identified to account for the development of high blood pressure. Nevertheless, in both types of hypertension, the phenotype is exacerbated by sodium loading, and only careful study of the intermediate phenotype (in this instance, measurement of adrenal steroid production) allows the pathogenesis to be understood.

The same argument can be applied to human hypertension, and it would be naïve to anticipate that the same underlying mechanism was present in all patients with high blood pressure. However, careful study of subgroups might identify common mechanisms that account for the rise in pressure and offer guidance to the best therapeutic option. In this regard, the contribution of adrenal steroids deserves careful review. At a gross level, of course, corticosteroids clearly do have an important role in the development of hypertension. Patients with Addison’s disease are hypotensive, glucocorticoid excess in patients with Cushing’s syndrome is associated with high blood pressure, and the role of a major excess of aldosterone in classic Conn’s syndrome due to a solitary adrenal adenoma is clear. Recently, however, the straightforward differentiation of these forms of “secondary” hypertension from “essential” hypertension has been obscured by suggestions that primary hyperaldosteronism (PHA) is present in 10% to 15% of unselected patients with hypertension. In this article, we will review some of this evidence and consider whether this biochemical abnormality is consistent with other known genetic and physiological mechanisms.

Definition of PHA

Much of the recent debate regarding the true prevalence of PHA is influenced by the way in which the diagnosis is made. In earlier definitions, the syndrome was identified by the excessive autonomous secretion of aldosterone, leading to mineralocorticoid hypertension, characterized by suppression of renin, expansion of body sodium content, expansion of plasma volume, and a tendency to hypokalaemia. It should be recognized, however, that in a small proportion of patients (eg, those with renal impairment or with accelerated phase hypertension), these classic phenotypic features can be absent. In the majority of patients with aldosterone-producing adenomas in earlier studies, aldosterone was found not to be responsive to its usual trophin, angiotensin II, but followed a diurnal pattern entrained by adrenocorticotrophin (ACTH). Patients with nontumorous primary aldosteronism were shown to differ in this regard, in that aldosterone was still regulated by angiotensin II, albeit at a much altered set point from normal. This argument was used by Padfield et al,
years ago, to suggest that idiopathic hyperaldosteronism was not a clearly distinct entity from low-renin essential hypertension; this contribution deserves to be revisited. Again, there is now evidence that in a subset of patients with aldosterone-secreting tumors, angiotensin is still able to stimulate aldosterone, and this situation illustrates that the diagnosis of primary aldosteronism probably includes several different pathophysiological syndromes. True primary aldosteronism was held in earlier studies to be rare, although a large proportion of patients with hypertension in later life (perhaps up to 30%) were shown to have suppression of renin, consistent with expansion of body sodium content. However, introduction of the use of the ratio of aldosterone to renin (ARR) as a common screening test for primary hyperaldosteronism in the 1990s led to suggestions that the disorder was present in up to 15% of unselected patients. Such claims have been made by several groups, including Gordon et al (Brisbane) and McDonald (Lim et al; Dundee), and it is clear that in most series, a similar proportion of patients do, indeed, have an ARR that is outwith a rather arbitrary normal range (generally >750 when aldosterone is expressed in pmol/L and renin as renin activity). In some of the series, efforts have been made to ascertain whether aldosterone production is truly autonomous by performing suppression tests with fludrocortisone, and these have tended to support the notion that regulation of aldosterone secretion is abnormal. Nevertheless, in the majority of patients identified by a raised ARR, the real reason for the abnormality is the low level of renin, which dominates the ratio, a problem compounded by difficulties in measuring low levels of renin activity by using older assays. In many patients, the level of aldosterone is within the “normal” range, and it is not clear that they would fulfil earlier criteria for diagnosis of primary aldosteronism; indeed, it is uncertain how they differ from previously identified patients with low-renin essential hypertension. A recent review of the literature based on ARR measurements confirms that there is a lack of good studies that have validated the technique of measurement. Thus, it is evident that the ratio shows only that the relationship between the mineralocorticoid and its principal agonist is abnormal and should not be regarded as synonymous with primary aldosteronism, as defined by earlier criteria. Although some of this debate may be semantic, we believe that clarity of definition is important. We suggest that 2 key questions arise.

First, in hypertensive patients with a high ARR, is there clear evidence of hypermineralocorticoidism? As noted previously, patients with well-defined tumorous primary aldosteronism have a distinct elevation of exchangeable body sodium content. It is noteworthy, however, that patients classified as having “idiopathic hyperaldosteronism” had a lesser increase in body sodium (and higher plasma potassium concentrations) than those patients with distinct tumors, consistent with the notion that the 2 diagnoses were not synonymous. When older patients (>50 years) with essential hypertension have been studied, body sodium content is certainly higher than in matched normotensive controls but to a lesser degree than seen in patients with aldosteronism (either tumorous or idiopathic) who have similar elevations of blood pressure. These careful studies, carried out in the late 1970s, also demonstrated that there was a tendency for young hypertensive patients (<35 years) to have reduced body sodium content. However, no long-term studies have been carried out to identify whether body sodium content rises with age in individual hypertensive patients, perhaps due to a chronic resetting of the renal pressure/natriuresis relationship. Furthermore, the relationship between body sodium and the ARR has not been studied. Thus, there has not been a systematic study of body sodium in relation to the ARR in patients (of any age) with hypertension or in patients with presumed primary aldosteronism based on the ARR definition alone. These older data, however, indicate that not all patients with an elevated ARR can be assumed to have the same degree of mineralocorticoid excess. It should be noted that we focus in this review on aldosterone as the key regulator of sodium balance, which is clearly an oversimplification. For example, there is good recent evidence in low-renin hypertension that genetic variation in adducin relates to the phenotype, presumably by altering the pressure-natriuresis relationship. Furthermore, it is possible that impairment of renin release in older subjects (perhaps as a consequence of vascular disease) allows potassium to become the principal trophin for aldosterone. Thus, it is important to recognize that altered regulation of aldosterone is likely to interact with other mechanisms to result in a final phenotype of hypertension with a raised ARR.

Second, if we accept that aldosterone is higher than expected from the level of its principal trophin, angiotensin II, why is this so? In other words, why is the relationship between renin and aldosterone altered? Extrapolating from data in older, low-renin hypertensive subjects, we suggest that the prevailing aldosterone level might be higher than predicted from the sodium/volume/renin status and could certainly be seen as “inappropriate,” if not necessarily “autonomous.” Early hypotheses suggested that in low-renin essential hypertension (ie, including patients with a high ARR), aldosterone synthesis is more than normally sensitive to angiotensin II. However, evidence is sparse and inconsistent. There is some evidence of hypersensitivity in patient subgroups, but it does not appear to be a general finding. There remains a second possible explanation: that renin concentration is low because another agonist is exerting a disproportionate effect. One possibility (mentioned previously) is that plasma potassium is sustaining aldosterone secretion in these patients, but there is no evidence that potassium levels are systematically raised in patients with a high ARR. It should, however, be borne in mind that very subtle changes in potassium determine the relationship between angiotensin II and aldosterone and that the role of altered potassium homeostasis in sustaining the raised ARR requires further investigation. One alternative factor that regulates aldosterone secretion is ACTH, and this is addressed later. However, if it is the case that a variable fraction of aldosterone secretion is controlled independently of electrolyte balance and extracellular volume, then this will have possible long-term physiological consequences.

The preceding arguments are, of course, largely semantic. The patients identified by an elevated ARR have an inappropriate level of aldosterone for its principal trophin, angioten-
The adverse cardiovascular effects of aldosterone (on cardiac tissue, the central nervous system, and the kidney) are amplified by sodium loading. Furthermore, McDonald (Lim et al19) has reported that patients with a high ARR show a good hypotensive response with use of the mineralocorticoid receptor antagonist spironolactone. This finding supports the notion that aldosterone is an important contributor to the maintenance of hypertension in this circumstance and that the hormone might be causing cardiovascular damage. Thus, although the true prevalence of primary aldosteronism, as defined by earlier criteria, might be debated, it seems reasonable to concur that a significant proportion (perhaps up to 15%) of patients with hypertension have suppression of renin and altered regulation of aldosterone, so that plasma levels are higher than predicted from the prevailing renin. Such patients might well show an optimum blood pressure response to aldosterone receptor blockade and derive significant benefit in terms of target-organ protection.

It is unclear how these patients (classified now by a high ARR) relate to those with low renin described previously by Laragh (Niarchos et al13) and others—such patients were said to respond well to diuretic therapy. Aldosterone responsiveness to perturbations in sodium balance and to exogenous angiotensin II is abnormal in some patients with this phenotype, and there are recent data to show that the trait is heritable. Nevertheless, aldosterone concentrations in patients with low-renin hypertension are higher than predicted from the prevailing level of renin, and it seems likely that there is substantial crossover between the groups. If so, it is tempting to speculate that patients with a raised ARR form a substantial proportion of the group of older hypertensive patients categorized as having low-renin essential hypertension and that the prevalence of a raised ratio would be higher in older hypertensive patients compared with younger subjects. If so, the biochemical abnormality may be one that develops with time as part of the evolution of the hypertensive phenotype in individual patients. Studies that compare groups of patients of different ages and that follow up patients over time are clearly indicated.

In summary, although there might remain some uncertainty regarding the exact definition of primary aldosteronism and the significance of a raised ARR, better recognition that a high proportion of patients with hypertension have disproportionate aldosterone production identifies a more targeted therapeutic approach. It might be time to move away from categorizing such patients simply as having primary aldosteronism and to define patients by their response to aldosterone receptor blockade.

**Does Development of a High ARR Have a Genetic Basis?**

**Regulation of Aldosterone Synthesis**

Aldosterone synthesis is regulated in the zona glomerulosa of the adrenal cortex by angiotensin II and potassium, although a variety of other influences, including ACTH, are also important (for a review, see Jamieson and Fraser20). The synthesis of aldosterone is accomplished by a series of biochemical steps, catalyzed by cytochrome P450 enzymes. The key terminal steps involve 11-hydroxylation of deoxycorticosterone (DOC) to corticosterone, followed by sequential 18-hydroxylation and oxidation to yield aldosterone. A single enzyme, aldosterone synthase, carries out these conversions.21 In the zona fasciculata, parallel 11-hydroxylation of deoxycorticosteroid to cortisol is accomplished by the enzyme 11β-hydroxylase (Figure 1). These 2 enzymes, which have similar but not identical function, share major sequence identity at the amino acid level. This, in turn, reflects a great degree of homology (>95%) in the coding regions of their respective genes. Aldosterone synthase is encoded by CYP11B2, and 11β-hydroxylase, by CYP11B1; they are arranged in tandem 40 kb apart on chromosome 8 in humans.21 The role of this locus in hypertension is suggested by several lines of evidence. First, in the Dahl salt-sensitive rat, mutations in both CYP11B1 and CYP11B2 are responsible for the altered biochemical phenotype (raised aldosterone secretion and elevated production of 18-hydroxy-DOC) that is associated with the development of hypertension.1 Second, loss of function of 11β-hydroxylase accounts for the rare autosomal recessive syndrome of congenital adrenal hyperplasia, in which excessive production of DOC leads to mineralocorticoid hypertension in early life.22 Finally, a gene rearrangement in which the 5′ regulatory region of CYP11B1...
is attached to the coding region of CYP11B2 results in the rare autosomal dominant syndrome of glucocorticoid reme-
diable aldosteronism.\textsuperscript{2,24} Thus, there are several strands of
evidence that draw attention to this locus as a potential
candidate in more common forms of hypertension.

\textbf{Polymorphisms in CYP11B2 and Hypertension}

Over the last few years, studies have concentrated on 2
common polymorphisms associated with CYP11B2. One is a
single-nucleotide polymorphism in the 5' promoter region of
the gene at $-\!344$ (C-T) that alters a putative recognition site
for the transcription factor SF1.\textsuperscript{25} The immediate biologic
importance of this is unclear, as recent reports suggest that,
whereas binding of SF1 is reduced 4-fold by the change from
C to T, there is no discernible effect on gene transcription
studied in in vitro systems.\textsuperscript{26} The second involves intron 2 of
CYP11B2, which is replaced, in part, by the corresponding
intron from CYP11B1. The 2 polymorphisms are in close
linkage disequilibrium, so that the common haplotypes iden-
tified by us and others are T conversion (38%); C wild-type
(45%), and T wild-type (16%).\textsuperscript{27}

We initially reported that the T allele of this gene was
associated with increased urinary excretion of the aldosterone
metabolite tetrahydroaldosterone.\textsuperscript{27} Subsequent reports have
found higher plasma levels of aldosterone,\textsuperscript{28} although it is
important to point out that other findings are not consistent,
and some authors have found that the contrasting allele is
associated with raised aldosterone levels.\textsuperscript{29} The T allele and
intron 2 conversion have also been found to present more
frequently than expected in patients with essential hypoten-
sion by us and several other groups\textsuperscript{27,30}; again, however, it
should be noted that some authors have failed to find this
association. Nevertheless, we have independently verified the
association between this locus and blood pressure by demo-
strating an epistatic interaction between CYP11B2 and the Y
chromosome in a large Scottish population.\textsuperscript{31} More recently,
we have found that the T allele and intron 2 conversion are
increased only in hypertensive patients with a high ARR, and
that frequencies are normal in subjects with a normal ratio.\textsuperscript{32}

As with the other phenotypes discussed previously, there is
also lack of unanimity. Finally, others and we have found an
association between the T allele and the diagnosis of tumor-
ous primary aldosteronism.\textsuperscript{33,34} In summary, therefore, there is
a considerable body of data to link the CYP11B2 locus and
hypertension, particularly that associated with mineralocorti-
coid excess. However, the evidence that the polymorphism is
associated with significant excess aldosterone responsiveness
to trophins in normal subjects is less convincing. In a recent
and rigorous investigation of the heritability and genetic basis
of low-renin hypertension, Fisher and colleagues\textsuperscript{17} reported
that the variance in renin status attributable to familial factors
was $\approx 35\%$; the CYP11B2 SF1 polymorphism was not shown to
be a major determinant of this. Furthermore, the associa-
tion in patients with aldosterone-producing tumors might
seem, at first, paradoxical, because there is no a priori reason
to suspect that a polymorphism in a gene regulating aldoste-
rone production should predispose to the formation of a benign adenoma. However, we suggest in a subsequent
section that this may inform our understanding of the link
between low-renin hypertension, bilateral adrenal hyperpla-
sia, and aldosterone-producing tumors.

\textbf{CYP11B2 and Variation in 11-Hydroxylation}

In studying the physiological consequences of the poly-
morphism in CYP11B2, we have examined not only aldoste-
rone levels but also other adrenal steroids. We have consist-
ently found that the T allele and intron 2 conversion, reported
previously to be linked to hypertension in patients with a
raised ARR, are also associated with raised basal and ACTH-
stimulated levels of the 11-deoxysteroids, DOC and deoxy-
cortisol.\textsuperscript{35} In addition, urinary excretion of the principal
metabolite of deoxycortisol, tetrahydrodeoxycortisol, is in-
creased in comparison with subjects homozygous for the T
allele (Kennon et al\textsuperscript{36}). Others have confirmed this unex-
pected finding.\textsuperscript{37} Initially, the association appears para-
doical, because the regulation of DOC and deoxycortisol levels
reflects 11$\beta$-hydroxylation efficiency, and the finding sug-
gests that this is reduced in subjects carrying the T allele. The
molecular mechanism that accounts for this is not understood,
but it is possible that the polymorphism in the 5' regulatory
region of CYP11B2 is in close linkage disequilibrium with a
genetic variant that affects expression or function of the gene
encoding 11$\beta$-hydroxylase (CYP11B1). Definitive studies of
the pattern of variation across the entire locus are required to
clarify this.

\textbf{Implications of Altered 11$\beta$-Hydroxylation
in Hypertension}

The suggestion that the efficiency of 11$\beta$-hydroxylation
might be reduced in hypertensives is not new. In 1985, de
Simone and colleagues\textsuperscript{38} reported that ACTH-stimulated
plasma levels of DOC were increased in hypertensive patients
compared with controls. More recently, we have made a
similar observation in a group of hypertensive patients from
Italy, in whom the ratio of deoxycortisol to cortisol (provid-
ing a marker of 11$\beta$-hydroxylation) was increased.\textsuperscript{39} At
the time of these observations, the cause of the finding was not
known, although it was thought unlikely to be a consequence
of high blood pressure. However, we now propose that the
biochemical abnormality is related to variation at the
CYP11B2/CYP11B1 locus. This needs to be formally tested in
hypertensive patients, although our data in normal subjects
suggest that this is a distinct possibility. Of relevance is our
observation some years ago that there was a defect in adrenal
11$\beta$-hydroxylation in patients with primary aldosteronism, a
finding that we could not explain.\textsuperscript{40} However, regardless of
the cause, it seems unlikely that the minor increase in DOC in
this circumstance has a significant mineralocorticoid effect
(although the consequence of a minor increase sustained over
decades is unknown). Similarly, the increase in deoxycortisol
is not likely to have a direct biologic effect. However, a more
important result of the altered conversion of deoxycortisol to
cortisol will be a small fall in the amount of cortisol produced
in response to ACTH—this is most likely to be apparent at
times when ACTH levels are at their nadir (ie, around midnight).
In reality, normal feedback regulation will result in a
resetting of the relationship between ACTH and cortisol,
so that normal circulating levels of the glucocorticoid will be
maintained at the expense of a subtle increase in ACTH drive to the adrenal cortex. This might be associated with a minor amplification in the diurnal variation in ACTH and cortisol levels and an alteration in the usual ACTH/cortisol relationship. Sustained over a lifetime, this would be expected to result in hyperplasia of the adrenal cortex, and it is pertinent that historical pathologic studies of adrenal morphology describe adrenal gland hyperplasia in patients with hypertension.\textsuperscript{41,42} Importantly, ACTH (or other peptides derived from pro-opiomelanocortin) has trophic effects on both the zona fasciculata and zona glomerulosa; expression of a number of the genes necessary for aldosterone production, including steroidogenic acute regulatory protein, P450 side-chain cleavage (CYP11A), and P450-21 hydroxylase (CYP21), is responsive to ACTH, so that there would be a potential amplification of aldosterone synthetic capacity.\textsuperscript{43,44} Although ACTH is reported to cause only short-term stimulation of aldosterone secretion, experiments have concentrated on very unphysiological exposure of the adrenal to grossly excessive amounts of ACTH, in which aldosterone production decreases within a few days.\textsuperscript{45} It is noteworthy that in patients with ACTH-dependent Cushing’s disease, who have exposure of the adrenal cortex to stimulation by ACTH for a sustained period, aldosterone concentrations are neither diminished nor increased.\textsuperscript{46} In this circumstance, the secretion of 18-oxocortisol is also increased, confirming that chronic ACTH excess does not lead to downregulation of expression of CYP11B2.\textsuperscript{47} However, it might be that it is the combination of chronic ACTH stimulation and an additional factor (acting in an epistatic manner) that is necessary to account for relative aldosterone excess. The situation we propose, however, also differs from that present in patients with Cushing’s syndrome, being present throughout life, and being characterized by a very subtle increase in ACTH secretion that reflects a minor defect in cortisol synthesis. Thus, over a very long period, the genetic change in 11β-hydroxylation efficiency (acting in an additional environmental or genetic influence) might result in ACTH-dependent alteration (steepening of the dose-response relationship) of the response of aldosterone to angiotensin II and potassium. Again, there is circumstantial evidence that ACTH is involved in setting the sensitivity of this relationship; the angiotensin II/aldosterone response is blunted in hypopituitary patients.\textsuperscript{48} Furthermore, consistent with the idea that there is increased ACTH drive to the adrenal cortex in essential hypertension is a report of increased levels of dehydroepiandrosterone sulfate (an adrenal androgen) in hypertensive patients.\textsuperscript{49} It is also relevant that very early studies reported that a proportion of patients with essential hypertension showed a good blood pressure response to low-dose dexamethasone treatment, perhaps consistent with the notion that ACTH was sustaining production of a hypertensinogenic adrenal steroid.\textsuperscript{50} Although the precise mechanism of this was never established, it is of interest to speculate that subjects who responded in this way had the defect in 11β-hydroxylation that we describe. Interestingly, a similar suggestion that a pituitary-derived peptide might lead to adrenal hyperplasia and aldosterone excess in a subgroup of patients with aldosteronism was made >10 years ago on the basis of histological and biochemical data.\textsuperscript{42} Clearly, the aforementioned hypothesis focuses on a single genetic polymorphism, and it is accepted that essential hypertension is a polygenic (or oligogenic) condition. Other genes may interact in an epistatic manner to lead to the phenotype of hypertension with an elevated ARR. It is possible that in predisposed subjects, chronic and low-grade activation of the hypothalamic/pituitary/adrenal axis as a result of variation at the CYP11B2 locus leads to a gradual increase in aldosterone production, resulting eventually in suppression of renin and a high ARR. This proposed epistatic interaction is a testable hypothesis that needs to be examined.

**Disordered 11β-Hydroxylation: A Unifying Hypothesis in Primary Aldosteronism and Hypertension Associated With a Raised ARR**

We propose that a variation at the CYP11B1 locus, for which the polymorphism in CYP11B2 is a marker, causes a minor defect in 11β-hydroxylation. Over many years, this leads to an amplification of aldosterone production in response to a range of stimuli, including angiotensin II and potassium (Figure 2). Interaction with other genetic determinants that
control blood pressure and with other trophins that regulate aldosterone, such as potassium, will determine the eventual phenotype. In some subjects who lack other predisposing genes for hypertension and in the absence of dietary sodium excess, no particular abnormality may develop. However, in the presence of moderate dietary sodium excess and other permissive hypertension genes, one might predict the development of hypertension with a raised ARR. We predict that this phenotype would become more pronounced in an affected individual with time, possibly explaining some of the high prevalence of low-renin, diuretic-responsive hypertension in the elderly. Typically, it would be expected that the relationship between angiotensin II would be reset (to become steeper) and would remain positive (as has been shown to be the case in patients earlier classified as having aldosterone excess with bilateral adrenal hyperplasia). However, in some subjects, perhaps due to other environmental or genetic factors, progression to an adrenal nodule or tumor formation may occur, and in this circumstance, aldosterone would become truly autonomous. It is of interest that pathological studies in adrenal tissue removed from patients with apparent solitary adenomas show that there is often hyperplasia of the adjacent zona glomerulosa and formation of multiple nodules throughout the gland.49 It is also noteworthy that in some subjects, abnormal dynamics of regulation of aldosterone secretion persist after successful removal of an aldosterone-producing adenoma.50 This would support the suggestion that some patients with tumorsary primary aldosteronism may have a more general dysfunction of regulation of aldosterone synthesis. The development of a nodule might be accounted for by other independent factors that favor clonal proliferation of adrenal cortex cells, so that the coincidence of a predisposition to synthesize excess aldosterone would lead to the clinical presentation of tumorsary Conn’s syndrome.

**Practical Implications**

The above proposals suggest that the development of hypertension associated with a high ARR is a chronic process and that the pathophysiological basis is present throughout life. In patients with other genetic and environmental factors that favor development of hypertension, the aforementioned scheme offers an amplification mechanism that will gradually lead to increasing mineralocorticoid effects on the vasculature with time. Given that it is now accepted that aldosterone excess has adverse consequences on endothelial, renal, cardiac, and central nervous system tissues, early identification of subjects at risk of development of aldosterone-modulated blood pressure would be important. For example, such subjects could be offered lifestyle intervention (this may be a subgroup who would benefit particularly from dietary sodium restriction) or targeted pharmacotherapy with aldosterone receptor blockade. As we predict that the development of a raised ARR is a relatively late event in the pathological progression, genetic screening (perhaps with a combination of markers) might be a feasible option. However, it is important to recognize that several of the previously suggested proposals require more detailed investigation to confirm the pathological chain of events proposed, and this remains a major challenge for the hypertension research community.

**References**


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