

# Overview: Mechanisms of Hypertension: Cells, Hormones, and the Kidney

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Hypertension is the most prevalent treatable risk factor for stroke, coronary artery disease, and renal disease. Inadequately treated hypertension is also a significant risk factor for dementia. Despite the overwhelming evidence for the adverse effects of hypertension on health and the availability of effective therapy to treat hypertension, large population surveys demonstrate that BP is adequately controlled in only 34% of hypertensives (1). There are many reasons for our failure to successfully lower BP in all patients. One concern is that some patients are reluctant to take the several pills daily required to normalize BP in

most individuals with greater than stage 1 hypertension. Treatment algorithms based on current national guidelines tend to endorse a strategy that derives from evidence-based literature, demonstrating that certain drugs (*e.g.*, diuretics) are associated with reductions in important clinical outcomes such as MI, stroke, and death (1). Current guidelines do not recommend treatment strategies on the basis of a mechanistic assessment of elevated BP in individual patients because clinical trial data supporting such an approach are limited. Better approaches to individualizing antihypertensive therapy to achieve optimal clinical outcomes and optimal patient adherence are needed.

Fifty million Americans have hypertension, and at least 90% are believed to have essential hypertension, defined as hypertension without a known cause. This terminology underscores the limitations of our knowledge regarding the pathophysiol-

ogy of elevated BP in individual patients. Recent advances in our knowledge of monogenic, inherited forms of hypertension have provided a glimpse into the future when it may be possible to identify the specific genes, hormonal pathways, cellular events, and environmental factors that contribute to elevated BP in the individual patient.

Frontiers in Nephrology in this issue of *JASN* focuses on mechanisms involved in hypertension. Each manuscript addresses an important area of research that has advanced our knowledge of the understanding of the pathogenesis of elevated BP. Moreover, these investigations highlight several exciting possibilities for innovative and mechanistic-based treatment of hypertension that have the potential to improve our management of this important risk factor.

Freel and Connell's article focuses on aldosterone, one of the most interesting and important hormonal systems involved in sodium balance and BP. They provide a comprehensive review of the role of aldosterone and cortisol in hypertensive disorders, and they advance an innovative hypothesis implicating excess aldosterone production, driven by ACTH, in the pathogenesis of essential hypertension in subgroups of low-renin hypertension. There is renewed interest in the role of aldosterone due in part to recent studies suggesting that hypertension resulting from excess aldosterone (identified by an elevated aldosterone renin ratio [ARR]) is more common than previously thought (2). Another reason for renewed interest in aldosterone is the recognition that its fibrogenic actions contribute to the progression of renal disease, cardiac fibrosis, and possibly vascular remodeling (3).

Considerable efforts have been made over the years to identify a more prominent role for adrenal hormones in essential hypertension. Abnormalities of the adrenal cortex including hyperplasia and increased production of various adrenal steroids have been suggested to play a role in some cases of essential hypertension. Identification of the molecular basis for glucocorticoid remediable aldosteronism (4) and 11- $\beta$  hydroxylase deficiency (5), both rare monogenic hypertensive syndromes, lend support to the notion that the adrenal cortex may be pathogenetically involved in subgroups of essential hypertension.

Primary aldosteronism, due to a solitary functioning adenoma, and bilateral adrenal hyperplasia are well-recognized causes of secondary hypertension. The principle hormonal features are suppressed renin and augmented aldosterone secretion. Several investigators have proposed the notion that patients with low-renin essential hypertension may represent one end of this spectrum of

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hypertensive syndromes of altered regulation of renin and aldosterone characterized by suppressed renin and inappropriate aldosterone secretion. In support of this hypothesis are the observations that adrenal hyperplasia has been demonstrated in patients with low-renin essential hypertension and that, in some patients with presumed solitary functioning adenomas, more careful pathologic examination of the adrenal gland demonstrates hyperplasia, suggesting that a solitary adenoma may arise in an already abnormal gland (6,7).

Freel and Connell discuss a possible genetic basis and a mechanism for a subgroup of patients with low-renin essential hypertension and an elevated ARR. They summarize studies of polymorphisms in the CYP11B2 gene, which codes aldosterone synthase, and they suggest that these polymorphisms may play a role in the pathophysiology of hypertension characterized by an elevated ARR. Interestingly, they report that these polymorphisms are also associated with elevated basal and ACTH-stimulated levels of the 11-deoxysteroids, DOC, and deoxycortisol. They hypothesize that the genetic polymorphism in the promoter region of CYP11B2 is in close linkage disequilibrium with a locus in CYP11B1, which results in increased levels of 11 deoxysteroids. Their theory is that 11- $\beta$  hydroxylation is impaired, leading to increases in DOC and 11 deoxycortisol and slight reductions in cortisol. This in turn leads to increases in ACTH-driven zona glomerulosa hyperplasia and enhanced aldosterone secretion in response to other more conventional stimuli such as angiotensin II or potassium. This hypothesis is provocative and lends itself to further investigation. It is also important because it broadens our perspective of essential hypertension and proposes a more mechanistic approach to pathogenesis and certainly treatment. Both spironolactone and the newer selective aldosterone receptor antagonist eplerenone offer targeted approaches to therapy of aldosterone driven hypertension.

Endemann and Schiffren's article on endothelial dysfunction addresses a structural as well as a functional dimension of the hypertensive disease process. Their comprehensive review of endothelial dysfunction highlights an important pathway in the development of hypertension as well as in the progression of target organ damage. Endothelial cell dysfunction is characterized by reduced vasodilation, oxidative excess, increased inflammation, and thrombosis. Endemann and Schiffren discuss the complex interrelationships involved in these processes. They review the role of reactive oxidant species in nitric oxide production, leading to exaggeration of oxidant excess and increased generation of inflammatory mediators such as VCAM-1, ICAM-1, and MCP-1. They discuss the significance of asymmetric dimethylarginine (ADMA), a competitive inhibitor of eNOS that has been linked to endothelial dysfunction. Plasma ADMA levels have been measured in a variety of clinical conditions, such as renal failure, hypercholesterolemia, hyperhomocysteinemia, and hypertension, and may turn out to be a useful marker of vascular dysfunction. With respect to treatment, Endemann and Schiffren discuss the benefits of treatment directed at endothelial dysfunction, such as L-arginine, angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB), statins, and peroxisome proliferator-activated receptor activators alpha and gamma.

Endothelial dysfunction may be directly responsible for elevated BP itself, as well as for the long-term untoward vascular consequences of hypertension, particularly atherosclerosis. Rather than being unique to a specific type of hypertension, it represents a final common pathway of injury in all hypertensive conditions. Understanding the mechanisms involved in endothelial dysfunction, developing the technology to monitor endothelial function in a clinical setting and tailoring therapy to target specific aspects of endothelial dysfunction represent important challenges with the potential to have a significant benefit for patients with all forms of vascular disease.

Textor's article on ischemic nephropathy underscores the challenges and the advantages of a mechanistic approach to diagnosis and treatment of hypertension, in this case renovascular hypertension. True renovascular hypertension is characterized by hypertension that is a direct consequence of reduced renal perfusion, usually due to an obstructive lesion of one or more major renal arteries. The result is activation of the renin-angiotensin system and hypertension. When renal excretory capacity is compromised, for example, with a solitary kidney, or with intrinsic parenchymal renal disease, there may be considerable sodium retention that may also contribute to elevated BP. Renovascular hypertension, by definition, will improve, after successful revascularization, provided there are no intervening complications of the procedure. The potential for cure, or dramatic improvement, is a strong incentive for identification of patients with true renovascular hypertension; however, more recent clinical trials have demonstrated that with currently available antihypertensive agents, BP may be satisfactorily controlled without an invasive procedure (8). Textor discusses the complex clinical condition referred to as ischemic nephropathy, defined as renal dysfunction in association with obstructive renal artery lesions. The pathophysiology of ischemic nephropathy is not well understood, and it is likely that prolonged or repetitive ischemic episodes are only one component. This is underscored by the important observation that young individuals with fibromuscular disease, and significant renovascular hypertension almost never have clinically detectable renal dysfunction. Identifying older patients with atherosclerotic renovascular disease and renal functional impairment that may improve after revascularization is a major challenge. Renovascular revascularization is associated with morbidity, patients often have serious comorbid illness, and available clinical trials have reported less than dramatic rates of significant improvement in renal function (9). Textor emphasizes the need for better clinical trials to more precisely define the role of renal artery revascularization as well as aggressive medical management with particular attention to lipid lowering, hypertension control, and reduction of inflammation. Until such trials have been conducted, the clinician is challenged when forced to decide whether revascularization (either angioplasty or surgery) is appropriate treatment.

The articles that comprise this installment of *Frontiers in Nephrology* represent a comprehensive review of exciting directions being pursued to improve our understanding of mechanisms involved in hypertension. The therapeutic benefits of this approach are apparent. Freel and Connell's article high-

lights hypertension characterized by relative aldosterone excess and treatable by aldosterone blockade. Textor's article highlights the paradigm of hypertension characterized by excess AngII, treatable either by renal artery revascularization or medications that interrupt the renin angiotensin system. Endemann and Schiffren discuss the potential for targeting endothelial dysfunction in the treatment of hypertension and its complications. Continued emphasis on understanding mechanisms will hopefully lead to optimal BP control in all patients with hypertension.

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