COUNTERPOINT: ACTIVATION OF THE INTRARENAL RENIN-ANGIOTENSIN SYSTEM IS THE DOMINANT CONTRIBUTOR TO SYSTEMIC HYPERTENSION

Our discussion regarding the dominant mechanism responsible for hypertension calls to mind the famous poem, “The Blind Men and the Elephant,” by John Godfrey Saxe based on an ancient fable from India. In essence, the blind men described the elephant based on their specific encounter, thus concluding that the elephant was a wall, a spear, a snake, a tree, or a rope. The lesson is that our interpretations regarding a specific experience are very much dependent on how it presented itself. Because of my predoctoral and postdoctoral training experiences with Arthur Guyton (10) and the fact that my research has been highly focused on the cardinal role of the kidneys in the pathophysiology of hypertension, I support the concept that alterations in kidney function in hypertension are predominantly due to an inappropriately increased activity of the intrarenal renin-angiotensin system (RAS) (Refs. 12, 17, 19, 21). While the nervous system is important (4, 5), I contend that chronic activation of the sympathetic nervous system is not the dominant contributor to hypertension, but may also contribute to the activation of the intrarenal RAS that is characteristic of many forms of hypertension (3, 19, 22).

Hypertension is characterized by increased peripheral vascular resistance due to increased vascular smooth muscle contractile activity and endothelial dysfunction (15, 29), but it is more likely that the vasculature is the victim rather than the culprit of the injurious processes that occur in hypertension (27). The nervous system regulates blood pressure by integrating signals coming from all parts of the body and sending neural signals to various organ systems. However, there is limited evidence that chronic increases in sympathetic activity serve as the dominant contributor to most forms of hypertension. Because the neurocentric view is being addressed by Esler, Lambert, and Schlaich (6), I will defer further consideration of this issue to them. Nevertheless, it is important to point out that the successful treatment of resistant hypertension using catheter-based renal sympathetic denervation was restricted to selected patients that were resistant to standard therapy (14).

Through its multiple actions, the kidneys exert a predominant role to regulate arterial pressure (10, 12, 19, 24). Importantly, transplantation studies have demonstrated that the hypertension follows the kidneys (9). There are many models of hypertension that are genetically related to the spontaneously hypertensive rat. Halbank and colleagues (5) also showed that the activation of the intrarenal RAS that is characteristic of many forms of hypertension is more likely that the vasculature is the victim rather than the culprit of the injurious processes that occur in hypertension (27). The nervous system regulates blood pressure by integrating signals coming from all parts of the body and sending neural signals to various organ systems. However, there is limited evidence that chronic increases in sympathetic activity serve as the dominant contributor to most forms of hypertension. Because the neurocentric view is being addressed by Esler, Lambert, and Schlaich (6), I will defer further consideration of this issue to them. Nevertheless, it is important to point out that the successful treatment of resistant hypertension using catheter-based renal sympathetic denervation was restricted to selected patients that were resistant to standard therapy (14).

Through its multiple actions, the kidneys exert a predominant role to regulate arterial pressure (10, 12, 19, 24). Importantly, transplantation studies have demonstrated that the hypertension follows the kidneys (9). There are many models of experimental hypertension but most of them involve procedures or genetic manipulations that activate the RAS (8, 11, 13, 22, 23). While enhanced activity of renal sympathetic nerves contributes to the magnitude of the hypertension, the hypertensive response is only attenuated and the increases in intra-
renal ANG II are similar in denervated kidneys as in innervated kidneys (11). In chronic ANG II-infused rabbits, the hypertension was not altered by renal denervation and renal sympathetic nerve activity was not changed (2). Furthermore, there was a general augmentation of vascular reactivity leading to augmented depressor responses to ganglionic blockade, but there was not an increased renal sympathetic activity (18). These studies have not shown differences in renal sympathetic nerve activity among rabbits with various forms of hypertension (2, 18). Prior renal denervation did not blunt the hypertension, suggesting that the sympathetic nervous system does not exert a direct role in the development of ANG II-induced hypertension (18).

Derangements in kidney function that prevent maintenance of balance between salt excretion and salt intake vary from overt renal disease causing reduced excretory capability to transport derangements causing excess sodium reabsorption. Importantly, the studies of monogenetic diseases demonstrate that mutations associated with hypertension are consistently associated with altered tubular reabsorptive function (16). Liddle’s syndrome, characterized by overactive amiloride sensitive sodium channels in the principal cells of collecting ducts, is a classic example (26). These single gene mutations demonstrate that transport alterations can cause hypertension independent of neural contributions. Although most forms of hypertension involve multiple gene effects, the final consequences are strikingly similar in that an inappropriate stimulation of tubular reabsorption leads to sodium retention and hypertension (19, 22, 26). Inappropriate activation of the intrarenal RAS is a very powerful hypertensigenic mechanism because the pleotropic actions of ANG II lead to increased renal vascular resistance, decreased renal blood flow, and glomerular filtration rate, increased aldosterone release and increased fractional sodium reabsorption at both proximal and distal nephron segments (12, 17, 20, 24, 30).

Excess salt retention may also be caused by derangements in neurohormonal communication pathways that maintain normal renal function (19). When inappropriately activated, however, these signals may alter renal hemodynamics and/or tubular transport to prevent appropriate sodium excretion at normal arterial pressure. The excess salt and volume retention leads to increased arterial pressure which then elicits a pressure natriuresis response (Fig. 2), allowing the kidneys to restore sodium homeostasis but at the cost of an elevated arterial pressure (19, 22).

The RAS has a powerful role because it is both an intrarenal system and a powerful extrarenal system that influences essentially every organ system (20, 24). In addition to the liver, the proximal tubular cells also produce abundant angiotensinogen that help maintain intratubular and renal interstitial ANG II concentrations greater than those in the systemic circulation (12, 25, 28). Furthermore, renin is formed in cells of the juxtaglomerular apparatus and also in principal cells of the collecting ducts, allowing secretion into the tubular fluid to form ANG I from angiotensinogen derived from the proximal nephron (23–25). Thus, the ANG II-mediated increased vascular resistance along with increased tubular reabsorption mediated by an augmented intratubular RAS leads to a sustained decreased sodium excretion and hypertension (10, 19).

An enhanced intrarenal RAS leads to enhanced ANG II throughout the body, thus contributing to increased cardiac contractility, increased peripheral vascular resistance, increased aldosterone release, and hypertensigenic actions throughout the body (3, 12). Importantly, the pressure natriuresis mechanism, which is responsible for restoring sodium balance when there is inappropriate salt retention (10), does not escape the powerful influence of an augmented RAS (17, 19). As depicted in Fig. 2, augmented intrarenal ANG II levels suppress sodium excretion at any arterial pressure (17, 19). Nevertheless, with sufficient increases in arterial pressure, the increases in sodium excretion restore sodium balance, but again only at the expense of an elevated arterial pressure. The dominant role of the RAS in hypertension is reflected by the fact that blockade of the RAS with ACE inhibitors, ARBs, or the newer renin inhibitor is rapidly being recognized as one of the most effective anti-hypertensive therapeutic strategies (1, 7).

**Conclusion.** In summary, many interacting physiological systems provide homeostatic regulation of arterial pressure, and derangements in any one of them can contribute to hypertension. While the nervous system provides regulatory inputs and stability to the blood pressure mechanisms, the primary responsibility for the long-term regulation of arterial pressure is vested in the kidneys’ capability to integrate endocrine, neural, and hemodynamic inputs to maintain sodium balance and arterial blood pressure. Of the many mechanisms contributing to these alterations, the RAS axis plays a most vital role in regulating both sodium balance.
and blood pressure through its pleotropic actions on multiple vascular, endocrine, and renal mechanisms. Accordingly, it is the intrarenal/intratubular RAS that is the final dominant arbiter responsible for hypertension!

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REBUTTAL FROM ESLER, LAMBERT, AND SCHLAICH

Dr. Navar candidly describes his lifelong professional interest in renal mechanisms of hypertension as originating from his mentorship by Arthur Guyton (9). The senior author also should come clean. In a medical undergraduate research year with Paul Nestel in 1966, he studied the sympathetic nervous system in patients with essential hypertension by measuring urinary norepinephrine excretion. For both the dye was cast early. Did these formative influences place Gaby, perhaps, on the wrong side of this debate?

My interest here has been in documenting neural causation of hypertension in humans, buttressed by research results from experimental laboratories, notably renal denervation experiments in animal models of hypertension (2).