Comments on Point:Counterpoint: The dominant contributor to systemic hypertension: Chronic activation of the sympathetic nervous system vs. Activation of the intrarenal renin-angiotensin system

ACTIVATED INTRARENAL RENIN-ANGIOTENSIN SYSTEM IS CORRELATED WITH HIGH BLOOD PRESSURE IN HUMANS

TO THE EDITOR: Dr. Esler (1) states that Dr. Navar did not provide evidence demonstrating that the activation of the intrarenal renin-angiotensin system (RAS) is the primary mechanism of essential hypertension in humans. However, recent clinical studies have provided data supporting the role of the intrarenal RAS in hypertension.

Studies by our group (2, 3) and others (4, 5) indicate that urinary angiotensinogen excretion rate provides a novel biomarker of the intrarenal RAS.

In a cross-sectional study, we reported that urinary angiotensinogen levels are significantly greater in hypertensive patients not treated with RAS blockers compared with normotensive subjects. Moreover, patients treated with RAS blockers exhibit a marked attenuation of this augmentation. However, patients treated with beta-blockers also exhibited high urinary angiotensinogen levels (2).

In a population study, we provided another example demonstrating that an activated intrarenal RAS is correlated with high blood pressure in humans. We recruited 251 subjects and collected a single random spot urine sample from each subject. Because urinary angiotensinogen levels are significantly increased in diabetic patients and the use of antihypertensive drugs affects urinary angiotensinogen levels, we excluded patients who had diabetes and/or were receiving antihypertensive treatment. Consequently, 190 samples were included for this analysis. Urinary angiotensinogen excretion rate provides a novel biomarker of the intrarenal renin-angiotensin system.

In controls. Plasma epinephrine concentrations were also similar, indicating that essential hypertension is not a disease of the mind. The high values of norepinephrine spillover reported by Esler et al. (2) could easily have been detected by 24 h measurements of urine norepinephrine and epinephrine. Again many authors have reported no difference in urine catecholamines between patients and controls. There is a characteristic difference in plasma volume in patients with pheochromocytoma compared with patients with essential hypertension. Patients with pheochromocytoma have a reduced blood volume due to the increase in blood pressure, whereas plasma volume is normal in patients with essential hypertension due to the increase in blood pressure. All these findings and others (5) suggest that essential hypertension is a disease of the kidney and it is not due to chronic activation of the sympathetic nervous system.

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SYMPATHETIC NERVOUS SYSTEM, PLASMA VOLUME, AND HYPERTENSION

TO THE EDITOR: Sympathetic activity may be measured by different techniques such as plasma norepinephrine, microneurography and spillover (3). A number of studies suggest that chronic activation of the sympathetic nervous system contributes to systemic hypertension (2). On the other hand, there are many carefully controlled studies, where no changes in sympathetic activity have been found (1). We studied, for example, plasma norepinephrine and renin in the basal state and after stimulation in a group of untreated patients with essential hypertension (4). Observed values were similar in patients and in controls. Plasma epinephrine concentrations were also similar, indicating that essential hypertension is not a disease of the mind. The high values of norepinephrine spillover reported by Esler et al. (2) could easily have been detected by 24 h measurements of urine norepinephrine and epinephrine. Again many authors have reported no difference in urine catecholamines between patients and controls. There is a characteristic difference in plasma volume in patients with pheochromocytoma compared with patients with essential hypertension. Patients with pheochromocytoma have a reduced blood volume due to the increase in blood pressure, whereas plasma volume is normal in patients with essential hypertension due to the increase in blood pressure. All these findings and others (5) suggest that essential hypertension is a disease of the kidney and it is not due to chronic activation of the sympathetic nervous system.

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SYSTEMIC HYPERTENSION—A “RATOLOGIST” POINT OF VIEW

TO THE EDITOR: It is reinvigorating to see that the debate on the pathophysiology of essential hypertension comes back into center stage, largely owing to the recent discoveries by the Professor Esler’s group (2). Evidence from rat models of essential hypertension can be taken to support both contentions (2, 6). An exhaustive review of the literature should include findings in the Lyon strain of genetically hypertensive (LH) rats. In this strain, it was found that early surgical denervation of the kidneys had minimal effects on adult blood pressure (1). It was also shown that neonatal chemical sympathectomy did not prevent hypertension and left ventricular hypertrophy in LH rats (5). By contrast, an early chronic treatment with an ACE inhibitor fully prevented the development of hypertension in LH rats. Furthermore, in ACE-blocked LH rats, a 4-wk infusion of angiotensin II, but not of noradrenaline, restored hypertension (4). Finally, it is of note that the renal and circulating renin-angiotensin system was found to be less active and less reactive (to both changes in renal perfusion pressure and β-adrenoceptor stimulation) in LH rats than in their normotensive controls (3). In LH rats, therefore, the renal renin secretion, although depressed, is still inappropriate considering the strong dependency of their blood pressure on the renin-angiotensin system. I would like to suggest that, while there might be different “dominant contributors” to high blood pressure in different strains of spontaneously hypertensive rats, this might also be the case in subgroups of hypertensive patients.

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SYSTEMIC HYPERTENSION—INVOLVEMENT OF THE CNS TO THIS COMPLEX PUZZLE

TO THE EDITOR: It has long been established that the two major contributors for systemic hypertension are the intrarenal mechanisms and the chronic activation of sympathetic nervous system (SNS) (1, 2). Both ideas were well discussed by Esler and Navar in the present issue of the *Journal of Applied Physiol*. However, it is important to consider that the central nervous system (CNS) highly contributes to systemic hypertension not only by controlling the sympathetic outflow specifically to renal territory but also to distinct territories, such as splanchnic, hindlimb, and cardiac that play a major role on regulation of vascular resistance and cardiac function (3). The precise mechanisms by which CNS regulates blood pressure (BP) are complex and remain to be discovered. Strong evidence has shown that manipulation of specific autonomic brain regions (hypothalamus, RVLM, and NTS) produces sustained BP and SNS changes in hypertension (3, 4, 5). Besides, it is also necessary to fit a new piece to this complex puzzle, with regards to neurochemical changes induced by proinflammatory cytokines in the hypothalamic-brain stem circuitry, which is linked to the control of the SNS that may lead to significant alterations in BP. Although we acknowledge the fact that the kidney plays a critical role in the long-term control of BP and the chronic activation of SNS is an important contributor to systemic hypertension, we conceive that new paradigms have to be taken into consideration to unravel the complexity of central modulation in the development and/or maintenance of high BP within the context of recent advances in cardiovascular and neuroscience research.

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CHRONIC ACTIVATION OF SYMPATHETIC NERVOUS SYSTEM AND SYSTEMIC HYPERTENSION—STRESS SHOWS THE WAY

TO THE EDITOR: In the Counterpoint rebuttal, Dr. Navar (5) states that “the divergence of opinion is whether singularly increased sympathetic nervous system activity, independent of activation of renin-angiotensin system (RAS), can result in sustained hypertension.” Despite the fact that it is difficult to dissociate increased sympathetic activity from activation of the RAS (3), the level of activity innervating different target organs can be non-uniformly changed, thus leading to different patterns according to particular stimulus (2). This is the case for mental stress, as pointed by Esler and colleagues (4). For example, mental stress in humans causes robust increase in muscle sympathetic nerve activity (1) that certainly may have chronic cardiovascular implications. We recently demonstrated that the control of sympathetic output by the dorsomedial hypothala-
mus (DMH), a critical nucleus for the cardiovascular response to emotional stress, is functionally asymmetric. Indeed, DMH exerts a strong influence over sympathetic activity to the kidneys and this outflow is predominantly lateralized (6). Central asymmetries also distinctly influence cardiac function, supporting the plausible hypothesis that central mechanisms differentially affect hemodynamic. Therefore, altered renal physiology is critical for the development of systemic hypertension, but this possibly results from chronic secondary activation of renal sympathetic outflow. Nowadays, the impact of psychosocial stress has undoubtedly been a challenge for the cardiovascular system and body homeostasis. Revealing the relevant central mechanisms involved in controlling sympathetic activity to acute and chronic stress is a critical step to understand the pathogenesis of essential hypertension.

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THE ROLE OF THE SYMPATHETIC NERVOUS SYSTEM—INFLUENCES OF SEX AND AGING

TO THE EDITOR: We congratulate Professors Esler and Navar on their excellent Point:Counterpoint on this long-running debate (2, 6). Our own perspectives lead us to support the primary importance of the sympathetic nervous system in human arterial pressure regulation. Along these lines, we offer additional thoughts in support of sympathetic neural mechanisms in control of arterial pressure in humans. Chronic levels of sympathetic nerve activity (SNA) are highly variable among individuals but reproducible in a given individual. In our recent studies, we demonstrated that this inter-individual variability in SNA is an important component of an integrated balance that includes cardiac output, vascular responsiveness, and sex differences (potentially via β-adrenergic receptors) that contributes to the long-term level of arterial pressure (1, 3). Thus it is interesting to note that, at least for men, SNA is inversely associated with the fall in blood pressure seen during ganglionic blockade (4). Observations from our laboratory and others suggest that, in aging humans, basal SNA becomes a crucial factor in determining the level of arterial pressure at rest (5).

This may be particularly evident in women: β-adrenergic-mediated vasodilation appears to blunt the pressor effects of SNA in young women (3), but may not offset these effects in post-menopausal women. Similar arguments may exist for nitric oxide-mediated vasodilation counteracting the pressor effects of SNA. In this context, the loss of nitric oxide bioavailability in conjunction with high levels of SNA might contribute to the genesis of hypertension.

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TO THE EDITOR: Debate continues (2, 5) about mechanisms of primary hypertension and the question of the relative roles of the sympathetic nervous and renin-angiotensin-aldosterone systems in chronic blood pressure regulation. This comment focuses more on the question than the answer. To study regulation of monitored variables such as blood pressure, physiologists use tools such as stimulation and ablation (4) or transgenic and knockout genetic analogs. Interpretations of results by these approaches often do not take into account principles of operation of homeostatic systems (3); because they do not do so, disputations such as this Point: Counterpoint will continue.

The first such principle is negative feedback regulation via multiple effectors. Effector redundancy affords clear natural selective advantages, including continued regulation of monitored variables via compensatory activation of alternative effectors if one effector fails. Compensatory activation, however, can obscure the role of particular effectors in regulation of a monitored variable such as blood pressure. The second principle is effector sharing. The renin-angiotensin-aldosterone system is a shared effector in homeostatic regulation of blood pressure and sodium homeostasis, and the sympathetic nervous system is a shared effector in regulation of blood pressure and core temperature. Because of effector sharing, blood pressure may or may not be correlated with renin-angiotensin-aldosterone or sympathetic nervous activity. Such correlations would
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depend on the status of the other homeostatic systems using those effectors.

Given the multiplicity of effectors regulating blood pressure, why does hypertension exist? The answer might come from better understanding about brain regulation of the renal function curve (1).

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TO THE EDITOR: This debate between Esler (4) and Navar (3) reminds me of a much earlier debate between Pickering and Platt (6). Pickering’s view was that hypertension is the upper end of the population blood pressure distribution and could be defined only by the blood pressure. Esler and Navar both subscribe to this model, focusing their discussion on the control systems that raise blood pressure and arguing whether the sympathetic nervous system (SNS) or the renin-angiotensin system (RAS) play a dominant role.

Platt, on the other hand, argued that there were two populations of patients, those with and those without hypertension. Blood pressures tended to be higher in the hypertensive population but could not be used to define the groups. The profession has disregarded the Platt viewpoint and limited its emphasis over the years to blood pressure.

Platt may not have understood how to distinguish his two populations, but recent data suggest it may be the artery wall. The functional and structural microvascular abnormality that accompanies hypertension appears to start with endothelial deficiency of bioactive nitric oxide. This deficiency results in microvascular changes that raise blood pressure (1). Both hereditary and environmental factors contribute to this nitric oxide deficiency. In the earlier phases of the disease, blood pressure is not necessarily above the threshold for the diagnosis of hypertension (5).

The SAS and RAS certainly influence blood pressure, and drugs that inhibit these systems will reduce blood pressure and protect the artery and heart from the deleterious effects of elevated blood pressure. But the disease likely begins with endothelial dysfunction, and the most effective therapies to reduce morbidity and mortality are those that restore endothelial function (2).

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TO THE EDITOR: Despite progress in genome technology, molecular genetics, and physiology, the underlying mechanisms causing elevated arterial pressure remain largely unknown. With this in mind, the academic debate concerning the “dominant” contributors to human essential hypertension (3, 5) is simply mind boggling and nothing but speculative. We recall that arterial pressure as a “phenotype” is polygenic and regulated by many pathways defined by a myriad of genes. As such, we agree that hypertension (2) is multifactorial in its etiology, with many and very different progression and pharmacologic response patterns.

Returning to the Point:Counterpoint series, standard clinical practice lacks the tools to differentially diagnose hypertension based on causal activation of either the sympathetic nervous system or components of a renal renin-angiotensin system. Rather than debating unknown relative contributions, we should comprehensively characterize patients to ultimately integrate genetics and physiology. This will allow us to distinguish between causal and secondary response mechanisms. Studies investigating pressor responses to monotherapies illustrate this dilemma. While individuals with high renin levels “respond” to renin inhibition, individuals with low renin show a “paradoxical” increase in pressure, suggesting that renin inhibition only interfered with an unaffected pathway that reset and thereby increased blood pressure further (1, 6).

We must progress toward complementing the intermediate phenotype “arterial pressure” with a combination of more informative biochemical and genetic markers, for diagnosis, treatment and drug development. Work by Laragh (4) has pointed us on the right path. Only the subclassification of hypertension will allow us to use the power of human genetics effectively and integrate genetics and physiology.

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DOMINANT CONTRIBUTORS FOR SYSTEMIC HYPERTENSION—WHO LEADS, WHO FOLLOWS?

TO THE EDITOR: The idea that disturbed renal physiology is critical for the development of systemic hypertension has been explored in two different views by Dr. Esler and Dr. Navar (1, 5). Dr. Esler argues that the dominant contributor to hypertension is the sympathetic nervous system (SNS), based on his promising results employing device-based therapy for treating drug-resistant essential hypertension in humans (1, 4). Dr. Navar rebuts Dr. Esler’s theory based on his experience built under Dr. Guyton’s philosophy on the pressure natriuresis mechanism for explaining hypertension (5, 6).

The renin-angiotensin inhibitors efficacy has been attributed in part by the actions on the neurally mediated renin-angiotensin system (RAS) activation. In addition, in multiple forms of experimental hypertension, renal denervation prevents or ameliorates the magnitude of hypertension by reducing renal sodium retention (2). On the other hand, absence of AT1 receptors in the kidneys markedly prevents the development of angiotensin- II infusions hypertension in mice (3), rebutting the neurogenic hypothesis that explains systemic hypertension.

At this point, the divergence of opinion will be sustained considering that interpretation of existing data is difficult because chronic activation of the SNS may cause activation of the intrarenal RAS, which leads to augmentation of the intratubular RAS and suppression of the pressure natriuresis mechanism as recognized by Dr. Navar. Besides, increased RAS could lead to chronic activation of the SNS as well. Therefore, both systems may share the credit or the guilt for the development of the systemic hypertension. However, the question regarding who leads and who follows still remains.

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OBESITY: A COMMON PRIME MOVER OF CHRONIC ACTIVATION OF THE SYMPATHETIC NERVOUS SYSTEM AND THE RENIN-ANGIOTENSIN SYSTEM IN SYSTEMIC HYPERTENSION?

TO THE EDITOR: Both debaters of the present issue admit that in addition to the chronic activation of the sympathetic nervous system, activation of the renin-angiotensin system may also contribute to the development and maintenance of systemic hypertension (2, 6). It is mainly the way they understand the word “dominant” that may be difficult to compare. A factor that is almost completely missing in either of the original

THE KIDNEY IS NOT ALWAYS THE TARGET IN NEUROGENIC HYPERTENSION

TO THE EDITOR: There is no dispute that increased renal sodium retention can lead to volume excess and elevated arterial pressure. The reviews by Drs. Esler (1) and Navar (5) find common ground on this point. However, we and others have questioned the so-called “renocentric” view that this is the only mechanism capable of causing hypertension. For example, hypertension caused by administration of angiotensin II in experimental animals has been suggested to be dependent, in part, on activation of the sympathetic nervous system (SNS). Dr. Navar dismisses this possibility since “renal denervation did not blunt the hypertension” (4), suggesting that the sympathetic nervous system does not exert a direct role in the development of ANG II-induced hypertension” (5). That is only true if one assumes that the only mechanism by which the SNS can cause hypertension is via neural control of the kidney. We do not share that assumption for the following reasons. We have also observed that renal denervation does not attenuate ANG II-salt hypertension; however, in the same study we reported that celiac ganglionectomy did, suggesting that the splanchnic vasculature, rather than the kidney, is the primary neural target in ANG II hypertension (2).

This conclusion is supported by our direct measurement of SNA in conscious rats, which shows that renal SNA actually decreases during ANG II administration (6), lumbrr SNA remains unchanged (6), whereas splanchnic SNA is increased (3). Therefore, activation of the SNS can cause sustained elevations in arterial pressure by targeting vascular beds other than the kidney.

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contributions is obesity, although it has been known for some time that excess weight gain is a major risk factor for essential hypertension and for end-stage renal disease, the latter being a major cause of hypertension on its own right irrespective of its origin or, conversely, obesity could be a major cause of renal insufficiency (4). It has been estimated that a high percentage of hypertensive cases may originate from morbid obesity and the sympathetic nervous system plays an important role in the development of obesity and, hence, in hypertension (1). Finally, in the background of hypertension induced by the accumulation of fat tissue the same endocrine factors seem to be functioning as those altering hemodynamics toward expansion of the extracellular space and increased responsiveness of the resistance vessels to vasoconstrictors (3). In fact, effects of increased renin activity, angiotensinogen, angiotensin II, aldosterone, as well as increased leptin level, insulin resistance, and inflammation may converge with an increased sympathetic drive, all factors having a similar prime mover in the form of obesity (5).

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CAROTID STIMULATION STUDIES SUPPORT A PROMINENT ROLE FOR THE SYMPATHETIC NERVOUS SYSTEM

TO THE EDITOR: The carotid baroreflex has been controversial since studies on sinoaortic denervation indicated that long-term blood pressure regulation was not under control of the baroreceptors (2). In addition, the arterial baroreceptors reset to sustained changes in pressure (1). Taken together, this evidence was convincing against the carotid baroreflex as a mediator of long-term control of blood pressure. In contrast, several recent studies on the carotid baroreceptors add new insight. Heusser et al. (4) report that one week of electric field stimulation of the human carotid sinus (i.e., stimulation of an increased pressure and stretch in the sinus) results in a sustained reduction in blood pressure and sympathetic nerve activity in resistant hypertensive patients. An important recent study by Lohmeier et al. (5) supports these observations and addressed both the effect of sustained sympathoinhibition by carotid stimulation and addressed the issue of baroreflex resetting. Lohmeier et al. demonstrated that after three weeks of electrical stimulation of the carotid sinus in dogs, there was no blood pressure compensation for the ongoing sympathoinhibition caused by the stimulation. This provides promising evidence that long-term carotid stimulation in humans (currently being tested in clinical trials) will improve blood pressure control in hypertensive patients. Together, these data indicate that 1) chronically lowering sympathetic outflow can cause sustained blood pressure reductions in hypertensive humans and 2) in contrast to the sinoaortic denervation models, these recent observations are highly supportive of a primary role for the baroreflex and sympathetic nervous system in long-term blood pressure control (3).

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TO THE EDITOR: It is well known that the kidneys are important organs in regulating sodium balance and blood pressure. Dysfunction of kidney can lead to hypertension. Of the many mechanisms contributing to these alterations, the intrarenal/intratubular renin-angiotensin system (RAS) plays a final dominant role (4). In ANG II-infused rats, renal sympathetic nervous activity decreased by 40% and then returned toward control levels (2). In Dahl salt-sensitive rats, salt sensitivity is associated with upregulation of the intrarenal angiotensin system (1). These data support the point that ANG II causes hypertension primarily through effects on AT1 receptors in the kidney, independent of actions of the sympathetic nervous system (2).

Nevertheless, activation of the sympathetic nervous system plays a critical role in some forms of hypertension. In high fat-fed rabbits, renal sympathetic nerve activity increased (5), suggesting the important role of sympathetic nervous system in obesity-induced hypertension. Dr. Esler considers that disturbed renal physiology is critical for the development of hypertension that results from chronic activation of the renal sympathetic outflow (3). However, not all activation of intrarenal RAS is dependent on activation of the renal sympathetic nervous system.

Multiple mechanisms are responsible for activation of intrarenal RAS or sympathetic nervous system in hypertension. It now seems likely that the roles of kidney and sympathetic nervous system are distinctive in different type of hypertension models. The reality is that we do not fully understand the mechanisms responsible for development and maintenance of hypertension.

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TO THE EDITOR: Focus should be on pertinence of methods, validity of conclusions, and recent conceptual changes favoring one or the other view.

From the Point contribution, the association between increased sympathetic drive and essential hypertension (EssHyp) (2) appears undeniable. The thesis of complete long-term baroreceptor adaptation is probably wrong (5); in contrast, the concept of differential sympathetic regulation of individual organs seems to be valid (3). In this setting, the results of renal nerve ablation are highly suggestive (2). But is a cause and effect relationship between sympathetic drive and EssHyp convincingly demonstrated? No.

Under the heading of "intrarenal RAS," Navar (4) describes the possible role of the kidney per se in EssHyp; with regard to the intrarenal RAS, the applied methods are not mentioned and the essential conclusions are less clear. The pressure natriuresis mechanism is in focus, although it is likely to be essential only when neurohumoral control systems are exhausted (1).

It may be appropriate to remember that 1) generally, animal models have not been very helpful in EssHyp research, 2) RAS variables should be quantified only during steady state on known electrolyte intake (6), and 3) faced with EssHyp, you cannot know what’s wrong, when it’s wrong, before you know how it’s right, when it’s right. Our level of ignorance with regard to the latter is frustrating. It would be ironic if brain and kidney each turn out to cause about one-half of the cases of essential hypertension.

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THE DOMINANT MECHANISM DEPENDS ON INDIVIDUAL CIRCUMSTANCE

TO THE EDITOR: While renal denervation effectively decreases blood pressure in pharmaceutical-resistant hypertension (3, 4), transplantation of kidneys from AT1-KO mice into wild-type mice has shown the essential role for intrarenal angiotensin AT1 receptors in establishing hypertension in response to elevated circulating angiotensin (2, 6).

Perhaps each of these mechanisms can play a dominant role depending on the individual circumstances of the patient or the model of hypertension. In the circumstance of renal ischemia or stenosis, renal denervation has been shown to reduce hypertension (4). Furthermore, there is evidence suggesting that, in addition to cutting sympathetic efferent drive, renal denervation reduces hypertension by preventing the afferent relay of a pressor signal arising from increased intrarenal release of adenosine (4).

In the circumstance of renal failure, it is possible that the two mechanisms operate in tandem to induce hypertension, where the pressor action of intrarenal angiotensin is transmitted via renal afferent nerves to stimulate hypertensive pathways via the brain (1).

The hypertensive action can also extend to other vascular beds, and it has been shown that angiotensin released by perivascular fat surrounding mesenteric vessels can increase smooth muscle contraction in response to neuronal stimulation (5).

Thus, depending on individual circumstance, consideration of the hypertensive mechanisms should include the influence of renal afferents and the stimulatory action of angiotensin on neurally mediated vasoconstriction in extrarenal vascular beds.

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REMODELING OF CENTRAL SYMPATHETIC CIRCUITS PRECEDES THE DEVELOPMENT OF HYPERTENSION

TO THE EDITOR: Chronic sympathetic activation and the renin-angiotensin system both play critical roles in the development and maintenance of hypertension (HTN) as thoroughly discussed by Esler and Navar (1, 4). Longitudinal studies following patients throughout the development of HTN, as well as advances in the measurement of sympathetic nerve activity (SNA) in juvenile HTN rats have strengthened the case for chronic SNA as the dominant contributor to the development of essential hypertension. Normotensive (NTN) subjects that developed HTN over a five-year period have greater plasmanorepinephrine concentrations prior to developing HTN than their NTN age-matched counterparts (3). In spontaneously HTN rats 9 days of age, thoracic SNA is significantly greater compared with age-matched NTN rats (5). The heightened SNA is not accompanied by changes in peripheral chemore-
SYMPATHETIC ACTIVATION IS THE DOMINANT CONTRIBUTOR TO SYSTEMIC HYPERTENSION

TO THE EDITOR: The role of the sympathetic nervous system in the development and maintenance of hypertension has been studied for over a century and there is increasing evidence showing that chronic sympathetic activation is a dominant contributor to most forms of hypertension in humans. We, therefore, support the concept of Esler et al (1). It is well known that hypertension is characterized by increased peripheral vascular resistance, which is attributable to increased vasoconstriction and endothelial dysfunction. Numerous studies have shown that activation of the sympathetic nervous system causes vasoconstriction through an alpha-adrenergic mechanism. Recent human research has found that sympathetic activation significantly decreases endothelial-dependent vasodilation and impairs endothelial function (3, 5). Conversely, previous studies have suggested that patients with essential hypertension with elevated plasma renin activity (an indication of increased renal sympathetic nerve activity) demonstrate features of sympathoexcitation when compared with hypertensive patients with normal plasma renin or normotensive individuals. However, we found in young and middle-aged moderate essential hypertensive patients that plasma renin activity was comparable to age, sex, and body mass index-matched normotensive controls at rest, yet muscle sympathetic nerve activity was significantly greater in these patients (2). Perhaps, more importantly, lowering the blood pressure resulted in dramatic sympathetic activation that was persistent (2), arguing that the baroreflex was regulating the blood pressure at this higher level. These results suggest that sympathetic activation to the skeletal muscle vasculature still exists even if sympathetic outflow to the kidneys may be within a normal range. One more example that supports the concept of Esler et al. (1) may be the findings of Schobel et al. (4), showing that pre-eclampsia (proteinuric hypertension) is a state of sympathetic overactivity, which reverts to normal after delivery. The study of Schobel et al. (4) indicates that the increases in peripheral vascular resistance and blood pressure that characterize pre-eclampsia are mediated by a substantial increase in sympathetic vasoconstrictor activity.

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AT1 RECEPTORS IN THE KIDNEY MEDIATE THE CHRONIC HYPERTENSIVE RESPONSE TO ANGIOTENSIN II

TO THE EDITOR: The remarkable efficacy of type 1 angiotensin (AT1) receptor blockers in lowering blood pressure in a broad spectrum of human hypertensive patients indicates that AT1 receptor activation is a critical mechanism underlying blood pressure elevation. To separate the contributions of AT1 receptors in the kidney versus all other systemic tissues to blood pressure elevation, we transplanted kidneys between genetically matched wild-type mice and mice lacking the dominant murine AT1 receptor isofrom, AT1\alpha. In this model, we found that mice with AT1 receptors in the kidney developed robust hypertension in response to chronic angiotensin II infusion, whereas mice lacking AT1 receptors in the kidney did not. The mice expressing renal AT1 receptors also had reduced sodium excretion and augmented total body weights early in the course of angiotensin infusion, suggesting that enhanced renal sodium reabsorption in these mice led to volume expansion (1). We interpreted these data to mean that activation of AT1 receptors in the kidney mediates the chronic hypertensive response to...
angiotensin II. We acknowledge that mice are not humans but also point to several kidney cross-transplantation studies in rodents and in humans that highlight the fundamental role of the kidney in persistent hypertension (2, 3, 6). Discriminating the role of the kidney versus the nervous system in the pathogenesis of hypertension has posed a challenge in part because the sympathetic nervous system can potentially influence the functions of the kidney through renal afferent innervation. Our experimental findings do not preclude the possibility that sympathetic neural activation in the setting of hypertension may indirectly trigger AT1 receptor activation in the kidney. In view of this possibility, we submit that when models of hypertension driven by modulation of neural outputs are employed, the regular inclusion of salt balance studies may be helpful in further characterizing the interaction between sympathetic outflow and renal sodium handling. Such an interaction would serve to reconcile the Guyton hypothesis (5) with the wealth of experimental data pointing to a role for the nervous system in hypertension.

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INTRARENAL ANGIOTENSIN II GENERATION AS A HYPERTENSINOGENIC MECHANISM

TO THE EDITOR: The importance of alterations in the renin-angiotensin system (RAS) in human hypertension has long been supported by the effectiveness of angiotensin-converting enzyme (ACE) inhibitors and AT1 receptor blockers to reduce blood pressure and slow the associated organ damage (3). However, as mentioned by Esler et al. (2), often human hypertensive patients lack consistent signs of systemic RAS activation (1). How can we reconcile such discrepancy? We would argue that the answer resides in alterations of tissue-specific RAS like the one in the kidneys. In support of this, recent clinical studies suggest that urinary angiotensinogen is increased in hypertensive subjects (6). If that holds true, blocking the enzymes responsible for intrarenal ANG II generation, like ACE, should therefore reduce blood pressure levels. On the other hand, enhancing intrarenal ACE activity should cause hypertension. We have generated evidence in favor of both cases. For the first instance, chronic ANG II-infused mice maintain renin and ACE activities in the kidneys despite a substantial suppression of plasma renin activity. If such mice are subjected to concomitant treatment with an ACE inhibitor, they failed to increase blood pressure (4). For the second case, mice with ACE expression restricted to the kidneys and simultaneous deletion from other tissues develop hypertension and increased intrarenal ANG II levels during chronic ANG I infusion (5). Is enhanced intrarenal ANG II generation the only mechanism by which all human subjects become hypertensive? Most definitely not; however, our results suggest that the intrarenal RAS can become an overriding mechanism in hypertension.

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SYMPATHETIC ACTIVATION: CAUSE OR CONSEQUENCE OF HYPERTENSION?

TO THE EDITOR: Among several mechanisms involved in the pathogenesis of human hypertension there are now two hypotheses in debate. One hypothesis is based on studies showing that the increase in sympathetic nerve activity (SNA; 2) to the kidney is a dominant contributor to systemic hypertension and the other theory supports the idea that the intrarenal renin-angiotensin system (RAS; 4) is the major contributor leading to the hypertension. Despite the fact that these two theories are apparently contradictory, in our point of view they are synergistic and might act in parallel not only to trigger but also to maintain hypertension. In fact, it has been demonstrated in activation of sympathetic nervous outflows to the kidneys, heart, and skeletal muscle vasculature in patients with essential hypertension (3). Several lines of evidence suggest that increased activity in afferents from diseased kidneys can act to increase SNA and hypertension. In patients with a slight reduction in creatinine clearance the sympathetic activity is already elevated (6). Other signals from the diseased kidneys, such as increases in angiotensin II, oxidative stress, and renal chemoreceptor activation, circulating levels of endogenous inhibitors of the nitric oxide synthase, salt intake, and citocines
may lead to sympathoexcitation (1, 5). However, not only
signals from the injured kidney but also others such as insulin
resistance and hyperleptinemia could increase SNA. Taken
altogether these studies demonstrate that even without a major
renal impairment the sympathoexcitation could be established
contributing to hypertension and further renal lesion.

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