Defect in the Sodium-modulated Tissue Responsiveness to Angiotensin II in Essential Hypertension

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ABSTRACT In normal subjects, dietary sodium intake modulates renovascular, adrenal, and pressor responses to infused angiotensin II (AII). To examine the hypothesis that this modulation is abnormal in some patients with essential hypertension, we studied 18 hypertensives and 9 normal subjects twice—during dietary sodium restriction and during loading. Paraaminohippurate (PAH) clearance was used to assess renal plasma flow. AII was infused in graded doses (0.3–3.0 ng/kg per min). Plasma aldosterone, cortisol, renin activity, AII, sodium, potassium, and PAH clearance were measured at the onset and end of each AII dose.

During dietary sodium repletion, eight of the subjects with essential hypertension showed a normal renovascular response (>125 ml/min per 1.73 m^2) to AII infusion (3 ng/kg per min). The decrement in renal blood flow in these normal responders (NR) was 168±10, which was comparable to the range in normotensive subjects (206±25 ml/min per 1.73 m^2). All of the remaining hypertensive patients, designated abnormal responders (AbR), had lower (<125) renal blood flow responses to the same dose of infused AII (mean decrement: 84±11 ml/min per 1.73 m^2) compared with the NR and normotensive subjects. Renal blood flow responses to all AII doses were statistically greater on a high-vs.-low salt diet in the NR ($P < 0.001$, chi-square) and normotensives ($P = 0.004$, chi-square) but sodium intake had no effect on this response in the AbR. Basal renal blood flow in NR increased significantly ($P < 0.001$, paired t test) with dietary sodium repletion, from 491±36 (low salt) to 602±40 ml/min per 1.73 m^2 (high salt), but was almost identical in the AbR on differing dietary sodium intakes (429±24 vs. 425±26 ml/min per 1.73 m^2).

The adrenal responses to sodium intake and infused AII also differed in the two subgroups. In the NR, the adrenal response to AII was significantly greater ($P = 0.011$, Wilcoxon signed rank test) after sodium restriction. In contrast, there was no significant difference in the aldosterone response to AII infusion between the low and high sodium diets in the AbR.

Thus, a substantial subgroup of essential hypertensives has an abnormality in responsiveness to AII in two systems central to volume homeostasis: the kidney and adrenal. They fail to modulate their renal blood flow and aldosterone responses to AII with changes in dietary sodium intake. Moreover, basal renal blood flow does not increase appropriately with increased sodium intake. These abnormalities, which may be due to an increased local production of AII or a defect in the AII receptors in these three target tissues, could contribute to the elevated blood pressure.

INTRODUCTION

Two abnormalities in effector systems critical to volume homeostasis have been documented in some patients with essential hypertension: some show a blunted aldosterone response to a volume deficit (1, 2) and some show a renal perfusion rate that is inappropriate for the level of sodium intake (3). The recent observation that both abnormalities occur in the same patient makes it possible that they share a common mechanism (4). Studies with angiotensin antagonists and converting-enzyme inhibitors have made it clear that angiotensin II (AII)[1] plays a dominant role in the normal response of both aldosterone release and renal blood flow to a

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[1] *Abbreviations used in this paper:* AII, angiotensin II; AbR, abnormal responder; FET, Fisher exact test; MCR, metabolic clearance rate; NR, normal responder; PAH, paraaminohippurate; PRA, plasma renin activity; WSRT, Wilcoxon signed rank test.

volume challenge; for example, to a reduction in sodium intake (5, 6). Sodium intake is also known to modulate the responses of both systems to AII (7–10). These observations placed a high priority on examining the responses of these two effector systems and the potential role of sodium modulation of these systems to AII in patients with essential hypertension—the subject of this study. The previous study (4) had made it clear that subgroups, rather than a continuum, were involved, and had classified the responsiveness of hypertensive patients as normal or abnormal on the basis of their adrenal response to acute stimulation on a low salt diet. The present study divided the patients according to their renovascular response to AII on a high salt diet (a condition that enhances responsiveness in normal subjects) in order to assess independently the linkage of the abnormality in these two target tissues.

METHODS

18 patients with normal- or high-renin essential hypertension and 12 normotensive subjects (age 18–45 yr) were studied on the Clinical Research Center of the Brigham and Women's Hospital. Among the hypertensives, patients with low-renin essential hypertension, defined as a plasma renin activity (PRA) response to upright posture on a 10-meq sodium diet of <2.4 ng/ml per h, were excluded (10, 11). Each hypertensive had had outpatient diastolic blood pressure measurements >90 mmHg on at least three occasions and documented evidence of hypertension for at least 6 mo before the study. Patients with renal disease, pheochromocytoma, Cushing's syndrome, and primary aldosteronism were excluded by urinalysis, serum creatinine, plasma aldosterone, plasma norepinephrine and epinephrine, and 24-h urine vanillylmandelic acid, norepinephrine, epinephrine, and 17-hydroxycorticosteroid levels. Renovascular hypertension was excluded by normal rapid-sequence intravenous pyelograms and ^{131}I-hippuran renograms. Two subjects underwent renal arteriography to eliminate this possibility definitively.

All antihypertensive medications were discontinued for at least 2 wk before the study. All hypertensive and nine of the normotensive subjects were fed constant isocaloric diets during their hospitalizations: one of 10-meq sodium and 100-meq potassium and the other of 200-meq sodium and 100-meq potassium. The order of diets was randomized. In some subjects, the study on each diet was performed during separate hospital admissions. Fluid intake was maintained at 2,500 ml/d. In three additional normotensive subjects, only a 200-meq sodium study was performed. Daily 24-h urine collections were analyzed for sodium, potassium, and creatinine. Each study was begun at 8 a.m., after the patient had been fasted and recumbent for 8 h. When the 18 hypertensive patients achieved metabolic balance on the 10-meq sodium diet, a posture study was performed. Control blood samples were drawn from the subjects while recumbent via an indwelling venous catheter. The subject then ambulated for 120 min, after which blood samples were collected. All samples were analyzed for PRA, AII, aldosterone, cortisol, sodium, and potassium.

Paraaminohippurate (PAH) infusion. All subjects underwent a basal PAH (Merck Sharp and Dohme, West Point, PA) infusion study after achieving metabolic balance on each diet. An intravenous catheter was placed in each of the subject's arms, one for infusion and the other for blood sampling. A control blood sample was obtained and then an 8-mg/kg loading dose of PAH was given. A constant infusion of PAH was immediately begun at a rate of 12 mg/min using an IMED pump (IMED Corp., San Diego, CA). This infusion rate achieved a plasma PAH concentration in the middle of the range in which tubular secretion dominates excretion. At this level, PAH clearance is independent of plasma concentration and, when corrected for individual body surface area, represents ~90% of effective renal plasma flow. PAH clearance was calculated from the plasma concentration and the infusion rate (12, 13). Plasma samples were obtained 45 and 60 min after the start of the constant infusion and steady state was achieved. The mean values were used for calculations.

AII infusion. After the assessment of basal PAH clearance, all subjects received an infusion of AII amide (Hypertensin, Ciba-Geigy Corp., Pharmaceuticals Div., Summit, NJ) at successive doses of 0.3, 1.0, and 3.0 ng/kg per min for 45 min each, using a Harvard infusion pump (Harvard Apparatus Co., Inc., Millis, MA). The constant infusion of PAH continued throughout the AII infusion to assess the changes in PAH clearance with increasing AII doses. Blood pressure was monitored every 2 min with an indirect recording sphygmomanometer (Arteriosonde, Roche Diagnostics Div., Hoffmann-La Roche Inc., Nutley, NJ) with the cuff positioned over the brachial artery of the arm containing the sampling catheter. Basal blood pressure was recorded for 1 h during the basal PAH clearance study. Blood samples were drawn at the end of the control period and after each incremental infusion dose of AII and analyzed for PAH, aldosterone, AII, PRA, cortisol, sodium, and potassium. All hypertensive subjects and nine of the normotensive subjects received PAH and AII infusions on both low and high sodium intakes.

Laboratory procedures. Blood samples were collected on ice, spun immediately, and the plasma was separated and frozen until the time of assay. Serum and urine sodium and potassium levels were measured by flame photometry, with lithium as an internal standard. Serum creatinine was measured by an autoanalyzer technique. AII, aldosterone, PRA, and cortisol were assayed by radioimmunoassay techniques that have been previously described (14, 15). Plasma PAH concentration was measured by a Technicon autoanalyzer spectrophotometric technique (12) (Technicon Instrument Corp., Tarrytown, NY).

The absolute average difference in paired PAH measurements on a single sample on the Technicon autoanalyzer on the same run is <1%. The internal standards vary by ~1% or less on different days. In a group of nine normal subjects in whom duplicate determinations of PAH clearance were obtained by this method on two different days while they were ingesting the same diet, the mean PAH clearance was 638±31 ml/min per 1.73 m^2. The absolute day-to-day variation was 30±39 ml/min per 1.73 m^2, an average of 4.7±6.0%. The moment-to-moment variation in paired samples drawn 10 to 15 min apart showed an average absolute variation of 7.2±9.7 ml/min, reflecting a percentage variation of 1.1±1.5%.

Group means have been presented with the standard error of the mean as the index of dispersion. Statistical probability was assessed with the t test for normally distributed data and the chi-square or Fisher exact test (FET) or Wilcoxon signed rank test (WSRT) for nonhomogeneously distributed data. Significant differences are at the $P < 0.05$ level, unless otherwise stated. The protocol was approved by the Human Subjects Committee of the Brigham and Women's Hospital.

Written informed consent for the procedures was obtained after full description of the protocol.

RESULTS

Hypertensive patients were grouped according to their renovascular response to the maximal AII infusion dose (3 ng/kg per min) on a high sodium intake. 10 of 18 had a smaller decrement than any of the 12 normotensives (<125 ml/min per 1.73 m^2) (Figs. 1 and 2). These subjects were designated abnormal responders (AbR). The rest were designated normal responders (NR). The mean decrement in renal blood flow in the normotensive, NR and AbR groups were 206±25, 168±10, and 84±11 ml/min per 1.73 m^2, respectively. The individual PAH clearance responses to infused AII show no overlap between the two hypertensive subgroups.

The hypertensives included in this study were sequential admissions, and the AbR did not differ significantly from the NR with respect to age, sex, admission blood pressure, duration of hypertension, serum creatinine, or any other identifiable physiological characteristic (Table I).

On AII infusion days, there was no significant difference between the normotensive subjects, NR, and AbR in urinary sodium or potassium excretion or serum potassium concentration (Table II). Mean body weight also was not statistically different between the NR and AbR on either the low or high sodium diets. Although the AbR tended, on the average, to gain more weight when they achieved high sodium balance (1.9 vs. 0.7 kg) than the NR, this difference was not statistically significant (unpaired t test). Mean supine PRA, AII, serum potassium, and diastolic blood pressure on the high or low sodium diet were not significantly different between the two groups of hypertensive patients. However, on a low sodium diet in the upright position, plasma aldosterone was significantly less ($P < 0.01$, FET) in the AbR (51±12 ng/dl) than in the NR (75±12 ng/dl), whereas upright AII levels were similar (102±17 vs. 92±28 pg/ml, respectively).

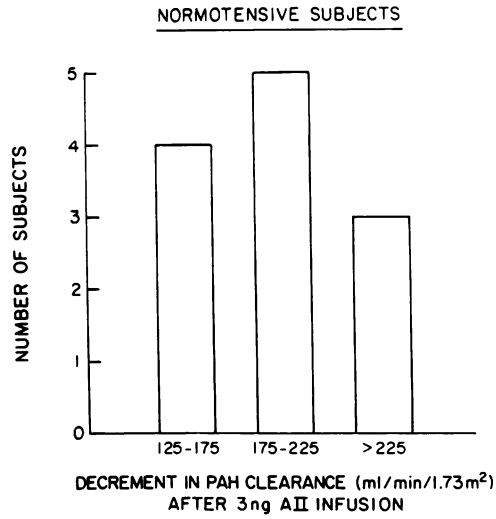

FIGURE 1 Frequency distribution of decrement in PAH clearance (milliliters per minute per 1.73 square meters) in sodium loaded (200 meq Na/100 meq K diet) normotensive subjects (n = 12) after maximal (3 ng/kg per min) AII infusion.

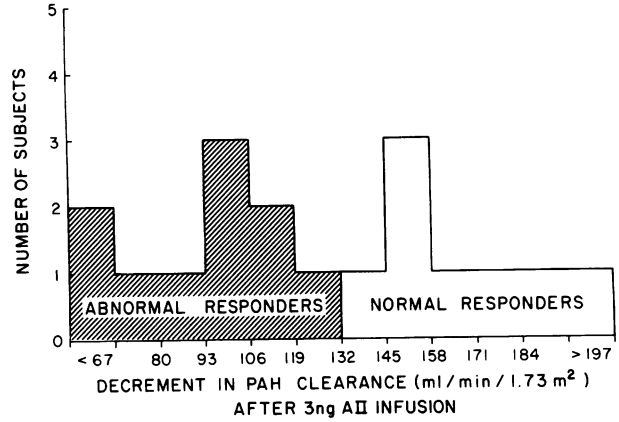

FIGURE 2 Frequency distribution of decrement in PAH clearance (milliliters per minute per 1.73 square meters) in essential hypertensives (n = 18) after 3 ng/kg per min AII infusion on a high salt diet. AbR (n = 10) are shown in striped area and their mean PAH decrement to 3 ng AII infusion was 84±11 ml/min per 1.73 m^2 (range: 26–120). NR depicted by open bars. Their sodium replete renal blood response to 3 ng AII infusion was 168±10 ml/min per 1.73 m^2 (range: 141–225), which was significantly greater ($P < 0.001$, unpaired t test) than that of the AbR.

Basal AII and aldosterone levels in the normotensive subjects were not significantly different from the hypertensive patients (Tables II, III), except for basal low salt aldosterone levels in AbR, which were statistically lower ($P < 0.01$, unpaired t test) than in normotensive subjects (13±3 vs. 29±5 ng/dl).

Renal blood flow responses. Basal supine AII levels were similar in the normotensive subjects, NR, and AbR after sodium restriction and loading. There were no statistical differences between the changes in supine plasma AII concentration among the normotensive subjects, NR, and AbR on either diet at any dose of AII infused (Table III).

The NR had statistically greater decrements in renal plasma flow on a high compared with a low sodium diet at all doses of AII ($P < 0.001$, chi-square), comparable to the responses observed in the normotensive subjects (Fig. 3). In contrast, the responsiveness of renal plasma flow to infused AII in the AbR was virtually identical on low and high sodium diets and equivalent

TABLE I
Characteristics of Hypertensive Patients

	NR	AbR
Mean age (*yr*)	41±6 (range, 18–69)	50±4 (17–63)
Number of subjects	8	10
Number of males	6	8
Duration of hypertension (*yr*)	5.4±1.32	7.2±2.2
Admission systolic blood pressure (*mmHg*)	146±5	156±4
Admission diastolic blood pressure (*mmHg*)	99±4	99±2
Admission serum creatinine (*mg/dl*)	1.0±0.1	1.2±0.1

Data are presented as mean±SEM.

to the responses of the normotensive subjects on a low salt intake.

Basal PAH clearances among the three groups of patients were compared on a high vs. low sodium diet. Normotensive subjects and NR both had a significant increase ($P < 0.01$, FET) in basal PAH clearance with a high salt intake (100±23 vs. 111±17 ml/min per 1.73 m^2). In contrast, high sodium intake did not modify basal PAH clearance in the AbR (−3±22 ml/min per 1.73 m^2) (Fig. 4).

Adrenal responses. The mean increments in plasma aldosterone in normotensives and hypertensives in response to infused AII are represented in Fig. 5. On a low sodium diet, the NR had a significantly greater ($P = 0.011$, WSRT) increment in aldosterone from control during AII infusion compared with their responses on

TABLE II
Base-line Data on Infusion Days

	NR (n = 8)	AbR (n = 10)
Dietary 10 meq Na and 100 meq K/d		
24-h urinary Na excretion (*meq*)	13±2	14±2
24-h urinary K excretion (*meq*)	68±9	71±5
Serum Na (*meq/liter*)	139±1	138±1
Serum K (*meq/liter*)	4.2±0.1	4.1±0.1
Body wt (*kg*)	88±5	85±3
Systolic blood pressure (*mmHg*)	126±4	120±4
Diastolic blood pressure (*mmHg*)	87±4	81±2
Basal PAH clearance (*ml/min/1.73 m^2*)	491±36	429±24
Basal supine PRA (*ng/ml/h*)	5.6±0.7	5.0±1.2
Basal supine plasma AII (*pg/ml*)	31±3	33±4
Basal supine plasma aldosterone (*ng/dl*)	16±3 ($P < 0.02$)	13±3
Creatinine clearance (*ml/min*)	105±10	102±6
Dietary 200 meq Na and 100 meq K/d		
24-h urinary Na excretion (*meq*)	197±28	196±14
24-h urinary K excretion (*meq*)	78±7	78±5
Serum Na (*meq/liter*)	138±1	140±1
Serum K (*meq/liter*)	3.9±0.1	4.0±0.1
Body wt (*kg*)	89.6±5.7	87±3
Systolic blood pressure (*mmHg*)	134±6	130±4
Diastolic blood pressure (*mmHg*)	88±5	86±1
Basal PAH clearance (*ml/min/1.73 m^2*)	602±40 ($P < 0.001$)	425±26
Basal supine PRA (*ng/ml/h*)	1.4±0.5	1.5±0.4
Basal supine plasma AII (*pg/ml*)	22±2	22±2
Basal supine plasma aldosterone (*ng/dl*)	4±1	3±1
Creatinine clearance (*ml/min*)	108±9	105±6

Data are expressed as mean±SEM.

TABLE III
Basal AII Levels and during Graded-Dose Infusion of AII

	Basal AII	Increment with AII		
		0.3 ng/kg/min	1.0 ng/kg/min	3.0 ng/kg/min
		pg/ml		
Normotensive subjects (n = 9)				
Low Na intake	41±5	4±1	11±3	34±5
High Na intake	25±3	8±3	13±3	46±7
Hypertensive subjects (n = 18)				
NR (n = 8)				
Low Na intake	31±3	5±3	12±2	39±5
High Na intake	22±2	2±1	9±3	48±12
AbR (n = 10)				
Low Na intake	33±4	4±2	19±7	53±11
High Na intake	22±2	4±1	9±1	45±5

Data are expressed as mean±SEM.

a high sodium diet as did the normotensive subjects. Aldosterone increments in the AbR, however, were not statistically different on the two diets at any dose of AII. Furthermore, on a low sodium diet, the adrenal response curve to AII in the AbR was significantly less (P = 0.03, chi-square) than in the NR or normotensive

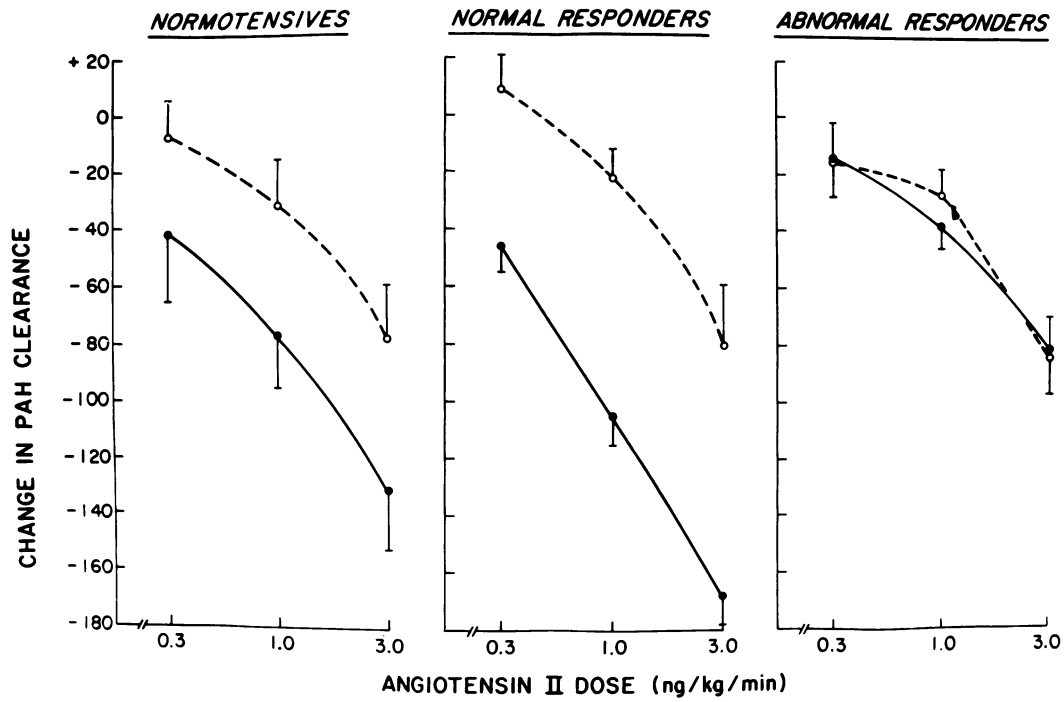

FIGURE 3 Comparison of mean±SEM responses in PAH clearance (milliliter per minute) during AII infusion in normotensives and hypertensives. The decrement in PAH clearance during AII infusion was significantly (P < 0.02) greater in the NR (*center* panel, n = 9) on the high (●) compared with the low sodium diet (○) comparable to the normotensive subjects (*left* panel, n = 8). There was no significant difference in PAH decrement during AII infusion for the AbR (*right* panel) between the low and high sodium responses (n = 10).

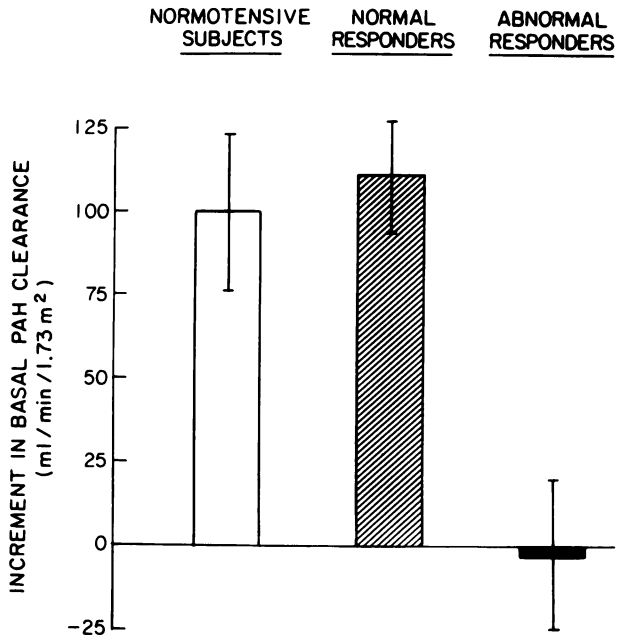

FIGURE 4 Increment in basal PAH clearance (milliliters per minute per 1.73 square meters) between sodium restricted and sodium loaded diets in normotensive and hypertensive subjects (mean±SEM). Basal PAH clearances increased significantly ($P < 0.01$, FET) with salt loading in normotensives and in NR but not in AbR.

subjects. Indeed, the low salt adrenal response in the AbR was nearly identical to the response of normotensives on a high salt intake.

Blood pressure responses. In contrast to the striking shifts in adrenal and renal vascular sensitivity to AII with changes in sodium intake, shifts in pressor responsiveness were more modest (Fig. 6). The NR displayed the anticipated enhanced response to AII on a high salt diet ($P < 0.01$; paired t test), but the AbR differed little from normal (Fig. 6). Pressor responsiveness, therefore, will not be useful in delineating subgroups.

DISCUSSION

In earlier studies of essential hypertensives, a blunted adrenal response to volume challenge was associated with reduced responsiveness to AII (16, 17). A more recent study has documented that some patients with essential hypertension have a blunted adrenal and renal vascular response to volume challenge, thus suggesting that an abnormality in responsiveness to AII could involve both the adrenal and the kidney (4). That possibility has been documented in this study. Subjects studied on high sodium intake, which ordinarily enhances renal vascular responsiveness, showed strikingly blunted renal blood flow responses to infused AII.

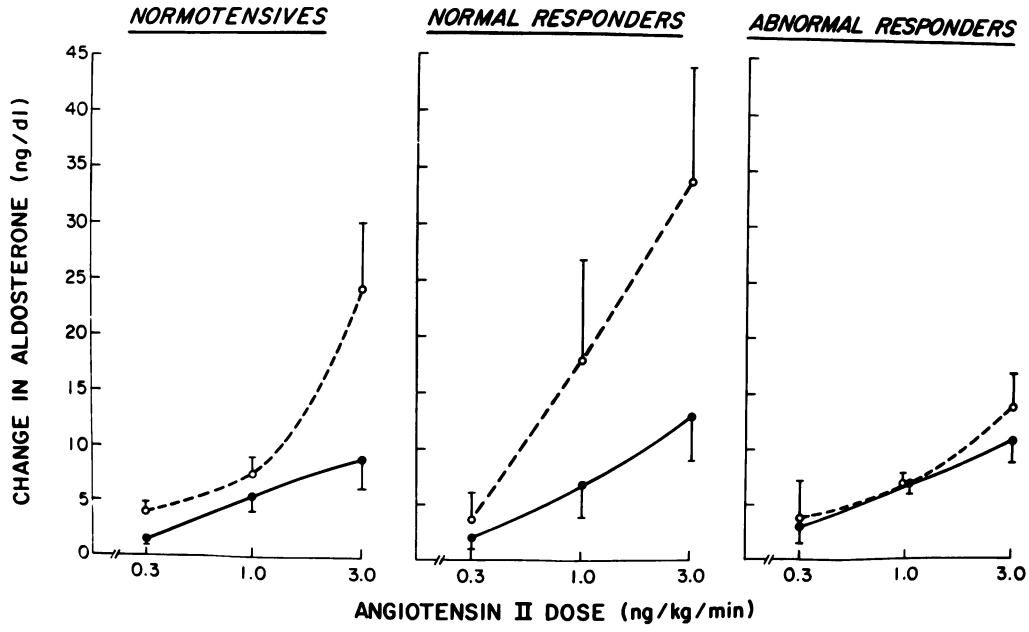

FIGURE 5 Mean±SEM incremental responses of plasma aldosterone to graded infusion of AII during sodium restriction (○) and loading (●) in normotensives and hypertensives. The aldosterone increment was significantly greater ($P = 0.011$) in the NR with sodium restriction than with sodium repletion (*center* panel, $n = 7$) comparable to normotensive subjects. The AbR showed no statistical difference between their aldosterone increments during sodium restriction and sodium repletion (*right* panel, $n = 10$).

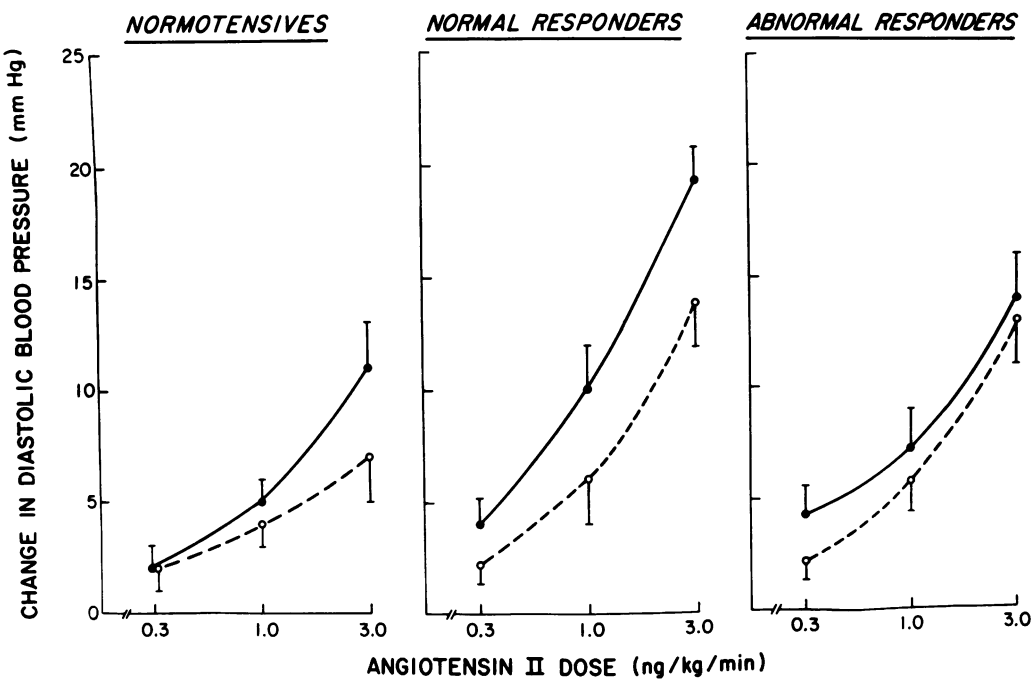

FIGURE 6 Mean±SEM incremental responses of diastolic blood pressure to infused AII on low (○) and high sodium diets (●) in normotensives and hypertensives. The increment in diastolic blood pressure in the NR (*center* panel) was significantly greater ($P < 0.01$) at the highest AII dose on the high compared to the low sodium diet ($n = 8$) similar to normotensive subjects (*left* panel, $n = 9$). There was no significant difference between the low and high sodium maximal blood pressure response in the AbR (*right* panel, $n = 10$).

Moreover, in earlier studies that examined the blunted adrenal response to volume challenge, separation of hypertensives into subgroups was based on their adrenal responses. This study, in which the separation of hypertensives into subgroups was based on their sodium replete renal vascular responses to infused AII, provides strong confirmation of the simultaneous occurrence of an adrenal and renal vascular abnormality in the same patient. Both systems share a blunted response to AII. For the adrenal, this abnormality is best recognized under conditions in which the adrenal responsiveness is maximized, i.e., a low sodium intake; for the kidney, the blunted response was evident under conditions that normally maximize renal vascular responsiveness, i.e., a high sodium intake. In the AbR, responsiveness of both systems did not vary with sodium intake. Thus, the normal modulation of effector system responsiveness to AII with changes in sodium intake is absent in these patients.

What factors could account for the differences in responsiveness to AII between the two groups of hypertensives? One might question the importance of age differences, because with increasing age beyond the fourth decade there is a gradual diminution of basal renal blood flow in normotensive subjects (18). Although the AbR tended to be older, the mean age between the two groups was not statistically different. Although basal renal blood flow tends to decline with age, up to 70 yr, its responsiveness to infused AII does not (18). Adrenal responsiveness to exogenous AII is also not modified by age in the age range spanned by the majority of our subjects (19). Differences due to age alone, therefore, could not produce these findings.

Another explanation might be that the AbR have more intrinsic renal impairment or more severe hypertension than do the NR. There were, however, no easily separable clinical differences in renal function, physical examination, electrocardiograms, duration of hypertension, or admission blood pressure between the two groups of patients. The subjects were similar as judged by clinical criteria.

Other factors that might account for the blunted aldosterone response to AII in the AbR are differences in serum potassium and adrenocorticotropic hormone secretion. In both groups of hypertensives, serum potassium levels were comparable and unchanged during AII infusion, and plasma cortisol levels declined in the normal diurnal fashion.

Our assessment of adrenal function might be criticized because plasma aldosterone concentration was

the sole index used. A difference in metabolic clearance rate (MCR) of aldosterone between the two groups of hypertensive subjects could lead to differences between basal and AII-stimulated aldosterone values. In addition, perhaps the AII infusion itself changed the MCR of aldosterone preferentially in one group of hypertensive subjects. The latter possibility is unlikely, because AII infusion alters the MCR of aldosterone similarly in essential hypertensives and normotensive controls (20). Furthermore, in a previous study in which both plasma aldosterone and secretion rates were used to assess adrenal responsiveness, these two parameters tracked together (4). Furthermore, in the present study, the upright low salt plasma aldosterone levels were significantly different ($P < 0.01$, FET) in the two subgroups with similar upright plasma AII levels, providing further support for a decreased adrenal response to AII in the AbR.

One might question whether the differences in basal levels of PAH clearance and aldosterone might determine the magnitude of responsiveness to infused AII. With this possibility in mind, we further subdivided the NR and AbR and compared patients in each group with statistically indistinguishable basal sodium replete PAH clearances and sodium-restricted aldosterone levels (Table IV). AbR had statistically lower renal blood flow ($P < 0.008$, FET) and aldosterone ($P < 0.03$, WSRT) responses to infused AII than did NR matched for comparable basal levels. This analysis suggests that differences in basal renal blood flow or aldosterone between the NR and AbR cannot explain the altered tissue responsiveness to AII.

Another methodologic criticism might be that steady-state plasma PAH determinations were used to assess renal blood flow uncorrected for PAH extraction by the kidney. However, renal extraction of PAH is constant until renal perfusion decreases to levels lower than those achieved with the highest doses of AII infused in this study (21), and clearly the basal levels of PAH clearance were well within the range in which extraction is unaltered. In addition, extraction of PAH by the kidney tends to be constant in the same individual, and in this study each hypertensive patient was studied serially on both diets. For these reasons, it seems acceptable to disregard PAH extraction by the kidney as significant.

None of the above criticisms, however, can account for the striking differences in renal vascular, adrenal, and blood pressure responsiveness to infused AII documented in the same patients in this study. What potential mechanisms could produce these abnormalities? An abnormality in the tissue concentration of AII or the AII receptor are obvious candidates. An enhanced renal vascular response to converting-enzyme inhibitors has been documented in essential hypertension (22, 23). This observation may illuminate a potential mechanism. Several investigators have observed in vitro and in vivo that vascular responsiveness to AII is regulated by local or circulating AII concentrations (24–26). Thus, one possible explanation for an unresponsive renal vasculature would be an inappropriately high level of AII in the kidney despite a high sodium intake. Such an inappropriately elevated intrarenal AII level could account for the blunted responsiveness to exogenous AII and the reduced renal blood flow response to sodium loading in the present study, as well as an enhanced response to converting-enzyme inhibition in the previous studies (22, 23). This explanation would make it unnecessary to account for the abnormality in the renal vascular response to AII on the basis of an abnormality in the AII receptor or a postreceptor event. However, such an explanation would not apply to the adrenal. Clearly, the best explanation would account for abnormalities in both systems on the basis of a single

TABLE IV
Comparison of Responsiveness to AII between NR and AbR with Similar Basal Renal Blood Flow or Plasma Aldosterone Levels

	Basal	Maximal change in response to AII infusion	
PAH clearance on high Na intake (ml/min/1.73 m²)			
NR ($n = 4$)	499±15	158±8	$P < 0.008$, FET
AbR ($n = 5$)	465±12	91±17	
Plasma aldosterone on low Na intake (ng/dl)			
NR ($n = 6$)	13±2	38±1	$P < 0.03$, WSRT
AbR ($n = 5$)	12±2	10±3	

Data are expressed as mean±SEM.

defect. The most plausible candidate is that of the AII receptor.

Another possible mechanism worth consideration is that the blunted responsiveness to AII reflects either an abnormal amount of sodium in the body or an error in volume perception. In previous studies, the majority of normal-renin essential hypertensives in low sodium balance failed to suppress PRA and aldosterone normally with saline infusion, suggesting an error in sodium or volume perception (27, 28). Several observations suggest that the potential defect does not reside here. Plasma volume measurements in two groups of hypertensive patients similar to the two reported in this study demonstrated no difference (4). In the current study, basal AII concentrations on a low or high sodium intake and upright AII levels during sodium restriction were similar in the NR and AbR, suggesting that neither the amount of total body sodium nor its perception was central to the derangement. Finally, in normal subjects, sodium intake reciprocally influences vascular and adrenal responses to AII: salt restriction blunts the vascular response, but salt loading blunts the adrenal response (7, 8). Thus, the subnormal responsiveness of both the adrenal and renal vasculature seen in the AbR could not be accounted for on the basis of an altered sodium space or abnormal volume perception. A more plausible explanation is that these hypertensives have lost the ability to modulate responsiveness to infused AII with changes in dietary sodium intake.

To determine how these abnormalities in renal blood flow and the adrenal could produce hypertension, one must examine the conditions under which the function of each is most critical. With dietary sodium loading, AbR show two differences from NR: (*a*) they fail to increase basal renal blood flow with the salt repletion; and (*b*) the absolute renal blood flow achieved is significantly less. Such differences theoretically would reduce the ability of the kidney to excrete sodium. An inability to excrete sodium appropriately might promote a volume-dependent form of hypertension. On the contrary, when dietary sodium intake is restricted in the Abr, the enhanced aldosterone response that normally facilitates sodium conservation is defective. The renin-AII-aldosterone volume feedback loop then could be closed only with excessive amounts of AII. On a low salt diet, the AbR might have AII-dependent hypertension. Thus, in the same individual depending on sodium intake, the hypertension could be either AII or volume dependent.

In support of the latter possibility, if hypertensives are first separated into normal-renin and high-renin subgroups, those subjects in each group with a decreased adrenal responsiveness to AII have a statistically greater PRA increment with upright posture than their comparable hypertensive control group (16, 29). Furthermore, in those hypertensive patients with a decreased adrenal response to AII, saralasin produces a substantially greater reduction in arterial pressure (similar to what occurs in patients with renovascular hypertension) than those who have a normal adrenal response (29).

If the AbR have AII-dependent hypertension, one might question why their circulating PRA and AII levels were not strikingly different from those of the NR. An analogy from clinical endocrinology may help to explain this observation. Proof of altered hormone production may be difficult to establish when the hormonal axis in question is evaluated in an unstimulated state. Thus, although in these hypertensives supine PRA and AII may be normal, blockade of the renin-AII-aldosterone system with saralasin might help to determine whether the hypertension is AII dependent. As noted above, these findings were reported previously in patients with decreased adrenal responsiveness to AII (29). Furthermore, if PRA levels are assessed after a more potent volume-depleting stimulus than used in the current study (upright posture and dietary sodium restriction), essential hypertensives with blunted adrenal responses to AII do have statistically greater circulating PRA levels (16).

This study raises an additional issue. Are the NR truly normal in their tissue responsiveness to AII? Although these subjects maintain sodium modulation of their renovascular, adrenal, and pressor responses to infused AII, the magnitude of their diastolic blood pressure responses is quantitatively greater than those of the normotensive controls suggesting they may not be normal. Unfortunately, the differences in pressor response to AII were insufficient to use this convenient index to separate the groups.

In conclusion, this study documents that in essential hypertensives there is an abnormality in responsiveness to infused AII in two systems central to volume homeostasis: the kidney and adrenal. Renovascular and adrenal responses to AII and basal renal blood flow in these patients are not modified by the level of sodium intake. Fortunately, possible underlying mechanisms and the relationship of the abnormality to the hypertensive process are both amenable to direct study.

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REFERENCES

1. Streeten, D. H. P., F. E. Schletter, G. V. Clift, C. T. Stevenson, and T. D. Dalakos. 1969. Studies of the renin-angiotensin-aldosterone system in patients with hypertension and in normal subjects. *Am. J. Med.* 46:844–861.
2. Williams, G. H., L. I. Rose, R. G. Dluhy, D. McCaughn, P. I. Jagger, R. B. Hickler, and D. P. Lauler. 1970. Abnormal responsiveness of the renin-aldosterone system to acute stimulation in patients with essential hypertension. *Ann. Intern. Med.* 72:317–326.
3. Hollenberg, N. K., and J. P. Merrill. 1970. Intrarenal perfusion in the young "essential" hypertensive: a subpopulation resistant to sodium restriction. *Trans. Assoc. Am. Physicians.* 83:93–101.
4. Williams, G. H., M. L. Tuck, J. M. Sullivan, R. G. Dluhy, and N. K. Hollenberg. 1982. Parallel adrenal and renal abnormalities in young patients with essential hypertension. *Am. J. Med.* 72:907–914.
5. Hollenberg, N. K., and G. H. Williams. 1979. Angiotensin as a renal, adrenal, and cardiovascular hormone: responses to saralasin in normal man and in essential and secondary hypertension. *Kidney Int.* 15:S29–S35.
6. Williams, G. H., N. K. Hollenberg, C. Brown, and J. H. Mersey. 1978. Adrenal responses to pharmacological interruption of the renin-angiotensin system in sodium-restricted normal man. *J. Clin. Endocrinol. Metab.* 47:725–731.
7. Oelkers, W., J. J. Brown, R. Fraser, A. F. Lever, J. J. Morton, and J. I. S. Robertson. 1974. Sensitization of the adrenal cortex to angiotensin II in sodium-deplete man. *Circ. Res.* 34:69–77.
8. Hollenberg, N. K., W. R. Chenitz, D. F. Adams, and G. H. Williams. 1974. Reciprocal influence of salt intake on adrenal glomerulosa and renal vascular responses to angiotensin II in normal man. *J. Clin. Invest.* 54:34–42.
9. Romero, J. C., R. J. Staneloni, H. L. Dufau, R. Dohmen, A. Benia, B. Kliman, and J. C. Fasciolo. 1968. Changes in fluid compartments, renal hemodynamics, plasma renin and aldosterone secretion induced by low sodium intake. *Metab. Clin. Exp.* 17:10–19.
10. Hollenberg, N. K., M. Epstein, R. D. Guttmann, M. Conroy, R. I. Basch, and J. P. Merrill. 1970. Effect of sodium balance on intrarenal distribution of blood flow in normal man. *J. Appl. Physiol.* 28:312–317.
11. Tuck, M. L., R. G. Dluhy, and G. H. Williams. 1975. Sequential responses of the renin angiotensin aldosterone axis to acute postural change: effect of dietary sodium. *J. Lab. Clin. Med.* 86:754–763.
12. Smith, H. W., W. Goldring, and H. Chasis. 1938. The measurement of the tubular excretory mass, effective blood flow and filtration rate in the normal human kidney. *J. Clin. Invest.* 17:263–278.
13. Schnurr, E., W. Lahme, and H. Kuppers. 1980. Measurement of renal clearance of inulin and PAH in the steady state without urine collection. *Clin. Nephrol.* 13:26–29.
14. Emanuel, R., J. P. Cain, and G. H. Williams. 1973. Double antibody radioimmunoassay of renin activity and angiotensin II in human peripheral plasma. *J. Lab. Clin. Med.* 81:632–640.
15. Underwood, R. H., and G. H. Williams. 1972. The simultaneous measurement of aldosterone, cortisol, and corticosterone in human peripheral plasma by displacement analysis. *J. Lab. Clin. Med.* 79:848–862.
16. Moore, T. J., G. H. Williams, R. G. Dluhy, S. Z. Bavli, T. Himathongkam, and M. Greenfield. 1977. Altered renin-angiotensin-aldosterone relationships in normal renin essential hypertension. *Circ. Res.* 41:167–171.
17. Dawson-Hughes, B. F., T. J. Moore, R. G. Dluhy, S. Podolsky, and G. H. Williams. 1981. Alterations in aldosterone biosynthesis in essential hypertensives. *Circ. Res.* 49:627–632.
18. Hollenberg, N. K., D. F. Adams, H. S. Solomon, A. Rashid, H. L. Abrams, and J. P. Merrill. 1974. Senescence and the renal vasculature in normal man. *Circ. Res.* 34:309–316.
19. Takeda, R., S. Morimoto, K. Uchida, I. Miyamori, and T. Hashiba. 1980. Effect of age on plasma aldosterone response to exogenous angiotensin II in normotensive subjects. *Acta Endocrinol.* 94:552–558.
20. Wisergof, M., and R. D. Brown. 1979. The metabolic clearance of aldosterone decreases similarly during infusion of angiotensin II in patients with essential hypertension and in normal subjects. *J. Clin. Endocrinol. Metab.* 49:107–109.
21. Smith, H. W., W. Goldring, H. Chasis, H. A. Ranges, and S. E. Bradley. 1943. The application of saturation methods to the study of glomerular and tubular function in the human kidney. *J. Mt. Sinai Hosp.* 10:59–108.
22. Williams, G. H., and N. K. Hollenberg. 1977. Accentuated vascular and endocrine response to SQ20881 in hypertension. *N. Engl. J. Med.* 297:184–188.
23. Hollenberg, N. K., L. G. Meggs, G. H. Williams, J. Katz, J. D. Garnic, and D. P. Harrington. 1981. Sodium intake and renal responses to captopril in normal man and in essential hypertension. *Kidney Int.* 20:240–245.
24. Williams, G. H., N. K. Hollenberg, and L. M. Braley. 1976. Influence of sodium intake on vascular and adrenal angiotensin II receptors. *Endocrinology.* 98:1343–1350.
25. Brunner, H. R., P. Chang, R. Wallach, J. E. Sealey, and J. H. Laragh. 1972. Angiotensin II vascular receptors. Their avidity in relationship to sodium balance, the autonomic nervous system, and hypertension. *J. Clin. Invest.* 51:58–67.
26. Gunther, S., M. A. Gimbrone, Jr., and R. W. Alexander. 1980. Regulation by angiotensin II of its receptors in resistance blood vessels. *Nature (Lond.).* 287:230–232.
27. Kaplan, N. H., and J. G. Silah. 1964. The effect of angiotensin II on the blood pressure in humans with hypertensive disease. *J. Clin. Invest.* 43:659–669.
28. Tuck, M. L., G. H. Williams, R. G. Dluhy, M. Greenfield, and T. J. Moore. 1976. A delayed suppression of the renin-aldosterone axis following saline infusion in human hypertension. *Circ. Res.* 39:711–717.
29. Dluhy, R. G., S. Z. Bavli, F. K. Leung, H. S. Solomon, T. J. Moore, N. K. Hollenberg, and G. H. Williams. 1979. Abnormal adrenal responsiveness and angiotensin II dependency in high renin essential hypertension. *J. Clin. Invest.* 64:1270–1276.