Reciprocal Influence of Salt Intake on Adrenal Glomerulosa and Renal Vascular Responses to Angiotensin II in Normal Man

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ABSTRACT The adrenal glomerulosa cell and the renal vasculature respond to similar arterial angiotensin II (A II) levels. We have assessed the effect of decreased sodium intake on their responses to A II in man. Studies were performed in 42 normal subjects in balance on a daily intake of 100 meq potassium and either 200 or 10 meq sodium/day. Renal blood flow was measured with ^{133}Xe and arterial A II, renin and aldosterone concentrations by radioimmunoassay. A II was infused intravenously (1, 3, or 10 ng/kg/min) for 40–60 min; 14 subjects received graded doses. The A II level increased linearly with dose and plateaued within 3 min; blood pressure and renal vascular resistance showed a similar time-course. Aldosterone rose within 10 and plateaued within 20 min. Dose-response relationships were established between the rate of A II infusion and the adrenal, the renal vascular, and pressor responses. Sodium restriction reduced the pressor ($P < 0.01$) and the renal vascular response ($P < 0.01$), but potentiated the adrenal response to A II ($P < 0.01$). An excellent correlation was found between the plasma A II and aldosterone levels, but the slope of their regression relationship on a high ($y = 0.13x + 6$) and low salt intake ($y = 0.32x + 14$) differed significantly ($P < 0.0005$). Thus, sodium intake reciprocally influences vascular and adrenal responses to A II: salt restriction blunts the vascular response and potentiates the adrenal's, a physiologically important influence in view of aldosterone's role in sodium conservation.

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INTRODUCTION

Among the host of pharmacologic actions that angiotensin II enjoys, at least two are likely to be important physiologically: angiotensin's effect on renal vascular smooth muscle and on aldosterone secretion. Both occur at normal angiotensin II blood levels (1–4). A major determinant of renin and aldosterone secretion is sodium intake (1–3), which also has a striking influence on renal vascular responses to angiotensin (4). In view of aldosterone's critical role in sodium homeostasis, there is surprisingly little agreement concerning the influence of salt intake on the adrenal's response to A II. For example, Ganong and Boryczka reported that a salt restricted diet in the dog potentiated the adrenal's response to angiotensin II (5). Mendelsohn et al., conversely, were unable to document such an influence of salt intake on adrenal responsiveness in man (6). In this study, we have taken advantage of recent improvements in the radioimmunoassay for plasma aldosterone and angiotensin II to explore the interaction between salt intake, the renal vascular and adrenal responses to angiotensin in normal man.

METHODS

Subjects and protocols. The studies were carried out in 42 normal potential kidney donors at the time of selective renal arterial catheterization for arteriography. Subjects ranged in age from 18 to 64 yr; each received a careful inpatient evaluation with special emphasis on cardiovascular, renal, and adrenal status to ascertain normality. Details of the clinical evaluation have been described (4). They were admitted to a metabolic ward, where each was placed on a controlled diet which contained a daily intake of 2,500 ml of water, 100 meq of potassium, and either 10 or 200 meq/day of sodium for 5 days before study. Balance was assessed by measuring sodium excretion in daily 24-h urine

collections and by a detailed daily dietetic assessment of intake.

The techniques for selective renal arterial catheterization, for determination of renal blood flow with radioactive xenon and external probe counting, and for cardiovascular monitoring during the administration of vasoactive agents (4) have been described in detail. In brief, percutaneous selective renal arterial catheterization was achieved with local anesthesia under fluoroscopic guidance. The catheter was used for the continuous monitoring of blood pressure and heart rate, for the injection of xenon, and for drawing arterial blood samples. Blood pressure was measured with a Statham P23Dc pressure transducer (Statham Instruments, Inc., Oxnard, Calif.) and recorded, along with the instantaneous pulse rate (cardiotachometer, Electronics for Medicine, Inc., White Plains, N. Y.) and the electrocardiogram, on an Electronics for Medicine recorder; continuous monitoring of these variables on a slave oscilloscope insured patient safety and cardiovascular stability. Mean blood pressure was calculated as the sum of diastolic and one-third of the pulse pressure.

At least 30 min elapsed after arteriography before the study was initiated. When the patient was stable and comfortable, a control blood flow determination was obtained and a control arterial blood sample drawn for the measurement of renin, angiotensin II, aldosterone, cortisol, sodium, and potassium. Arterial samples were used because they provide the best measure of the angiotensin II concentration approaching the adrenal and kidney and because the radioimmunoassay for angiotensin II is sensitive to the products of angiotensin degradation which are maximal in venous blood (7, 8). An intravenous infusion of angiotensin II (Hypertensin, Ciba Pharmaceutical Co., Summit, N. J.) was then initiated in 38 of the 42 subjects in 0.3–1.0 ml/min 5% glucose in water with a motor-driven syringe (Harvard Apparatus Co., Inc., Millis, Mass.). The syringe was marked at intervals to insure a constant infusion. In 24 subjects, 12 on each diet, a single dose (1, 3, or 10 ng/kg/min) was infused. Thus, four subjects on each diet received one of the three doses. Serial samples and blood flow determinations were obtained at 3, 10, 20, 30, and 40 min, and in five cases, 60 min after the initiation of the angiotensin infusion. In 14 additional subjects, 7 on each diet, a dose-response relationship was obtained by increasing the infusion rate from 1 to 3 ng/kg/min after 20 min. Samples and blood flow determinations were obtained at the end of each 20-min infusion. In two others, an identical study was performed with an intravenous infusion of 5% glucose in water, but without angiotensin. In another two, angiotensin II was infused into the renal artery distal to the adrenal artery at 1 ng/kg/min for 20 min, and arterial samples were drawn immediately after the infusion.

Analytic techniques. All blood samples were collected on ice, immediately spun, and the plasma was separated and frozen until the time for assay. Samples for plasma renin activity (PRA) and angiotensin II levels utilized EDTA as the anticoagulant; heparin was used in the samples for cortisol and aldosterone. Diisofluorophosphate was also added to the samples for angiotensin II assay. Sodium and potassium in urine and blood were measured by flame photometry, with lithium as an internal standard.

Plasma aldosterone and cortisol were measured by displacement analysis techniques as previously described (9). In brief, the plasma was extracted with methylene chloride, chromatographed in a Bush 5 system (G. F. Bush Associates, Princeton, N. J.), and the steroids were eluted. Aldosterone was determined by radioimmunoassay using an antibody specifically directed against it. Cortisol was measured by a competitive protein-binding method. The levels found in the plasma of adrenalectomized subjects were below the sensitivity of the method for cortisol and at the 2 pg/4 ml level for aldosterone. The sensitivity of the cortisol assay system was 0.2 ng/binding tube, and for aldosterone, 0.002 ng/binding tube. The coefficient of variation was between 7 and 11% at a level 10 times the sensitivity for the 2 assays. Recovery of added steroid from each assay was the same, ranging from 85 to 110%.

Angiotensin II values were measured by a double-antibody radioimmunoassay method (10). This assay was sensitive to a level of 7 pg/ml, with a coefficient of variation at the 20 pg/ml level of 6.8%. Recoveries of added angiotensin II at three different levels ranged from 88 to 108%. PRA was measured by radioimmunoassay of angiotensin I generated during a 3-h incubation with endogenous substrate (10).

Mean renal blood flow was measured from the initial slope of ^{133}Xe disappearance from the kidney, determined graphically with a hematocrit-corrected partition coefficient; compartmental analysis was also performed (4). Curves reanalyzed on a coded basis showed a coefficient of variation of 7%.

Group means have been presented with the standard error of the mean as the index of dispersion. The evaluation of statistical probability was carried out, where appropriate, with the Student's t test or paired data t test—corrected by Dunnett's convention (11). Otherwise, the Wilcoxon rank sum (WRST) [1] or Fisher direct probability tests (FDPT) for nonparametric data were used. The null hypothesis was rejected when the P value was less than 0.05.

The protocol was approved by the Human Experimentation Committee of the Peter Bent Brigham Hospital. Written permission for the procedure was obtained after a careful description of the protocols in every case.

RESULTS

Responses to restriction of sodium chloride intake. The characteristics of the subjects are summarized in Table I. The two groups did not differ with respect to age, weight, sex distribution, blood pressure, or any identifiable physiological characteristics on admission. Achievement of sodium balance was associated with a significant fall in body weight, from 73.2±2.8 kg (t, paired data = 9.7; $P < 0.001$). The subjects excreted 190±21 meq of sodium in excess of intake during the 5 days when balance was achieved. Serum sodium and potassium concentrations were not statistically different when balance was achieved, but a significant increase in the serum creatinine concentration was evident ($P <$ 0.025). Serum creatinine concentration was identical in the two groups (1.0±0.05) on admission. Similarly, the effect of sodium restriction was evident in the 24-h urine sodium excretion, which closely matched intake (Table I). Systolic and diastolic blood pressure tended to be lower in the group on a low salt intake, but this did not achieve statistical significance. Renal blood flow

[1] *Abbreviations used in this paper:* FDPT, Fisher direct probability test; WRST, Wilcoxon rank sum test.

TABLE I

Characteristics of the Sodium-Restricted and Replete Subjects when Balance Achieved

	Sodium intake/24 h		
	200	10	*P*
Number			
Males	14	13	
Total	19	19	
Weight, *kg*			
Admission	73.3±2.9*	73.2±3.0	NS
Study	73.0±2.8	71.2±2.8	NS
Age, *yr*	41.1±2.9	43.1±3.7	NS
Serum sodium, *meq/liter*	144.0±0.7	142.4±0.65	NS
Serum potassium, *meq/liter*	4.40±0.11	4.5±0.08	NS
Serum creatinine, *meq/liter*	0.96±0.05	1.11±0.04	<0.025
24-h urine sodium, *meq*	193±14	14±3	<0.001
Blood pressure, *mm Hg*			
Systolic	112±4.0	109±4.8	NS
Diastolic	60±2.3	58±1.5	NS
Mean renal blood flow, *ml/100 g/m*	398±11	356±15	<0.01
Serum angiotensin II, *pg/ml*	21.0±1.3	52.3±6.0	<0.01
Plasma renin activity, *ng/ml/h*	1.1±0.5	5.2±0.8	<0.01
Aldosterone, *ng/100 ml*	5.6±0.5	25.6±3.6	<0.01

NS = $P > 0.05$.

* Mean±SEM.

at the time of the study, however, was significantly reduced in the sodium restricted group (356±15 vs. 398 ±11 ml/100 g/min; $P < 0.01$). Similarly, restriction of sodium intake was associated with a highly significant increase in plasma renin activity, angiotensin II, and aldosterone concentrations ($P < 0.01$). A 2.5-fold increase in the plasma angiotensin II concentration (52.3 ±6.0 vs. 21.0±1.3 pg/ml) was associated with a 5-fold increase in the plasma aldosterone concentration (25.6 ±3.6 vs. 5.6±0.5 ng/100 ml).

Responses to angiotensin infusion. Angiotensin infusion was associated with a series of reproducible responses. A prompt dose-related increase in the arterial angiotensin II concentration was evident within 3 min (Fig. 1). Thereafter, there was a tendency to a small increase over the following 40–60 min (t paired data for 3 vs. 40 min = 2.44; $P < 0.025$). The relationship between dose, salt intake and blood level achieved at 20 min, the midpoint of the infusion, is shown in Fig. 2 and is summarized for the group receiving the graded infusion in Table II. In Fig. 2 the 20-min data for the 2 groups has been pooled, and thus, there are 11 subjects on each diet for the 1 and 3 ng/kg/min doses; 4 received the 10 ng/kg/min dose. Pooling is justified, because significant differences in the parameters measured were not found for either dose in the groups receiving a single dose, and in those on whom a graded infusion was performed. Differences between the increase in angiotensin II blood level in the group in balance on a high and low sodium diet were small and random.

In subjects on a low sodium intake, mean blood pressure did not rise by more than 10 mm Hg, and blood pressure variations showed no relationship to dose. In the subjects on a high salt intake, however, there was a significant ($P < 0.01$) dose-related increase in mean blood pressure (Fig. 2). The response was generally maximal within 3 min and stable thereafter. A good correlation was found between diastolic pressure (y) and the angiotensin II blood level ($y = 0.053x + 64$; $r = 0.78$; $F = 111$; $P < 0.001$) in the subjects on a high salt intake. When mean blood pressure rose by 10 mm Hg or more, it always fell to near control levels within 3 min of stopping the infusion: this was characteristic of the sodium-replete subjects receiving 3 or 10 ng/kg/min. The largest blood pressure increase that occurred was from 120/60 to 160/90.

The subpressor dose of angiotensin II, 1 ng/kg/min, produced a highly significant reduction in renal blood flow within 3 min in both groups ($P < 0.01$; Fig. 1). Larger doses produced a progressively larger response (Fig. 2). The responses at all doses was significantly reduced in the subjects on a low salt diet ($P < 0.01$; WRST). Moreover the renal vascular response tended

to be better sustained in the sodium-replete subjects, although the trend did not achieve significance ($P = 0.08$; FDPT).

Conversely, as evident in Fig. 2, the increase in plasma aldosterone level was accentuated at all dose levels in the subjects in balance on a low salt diet ($P < 0.01$; WRST). The arterial plasma aldosterone level began to increase within 3 min and increased progressively to 20 min. Thereafter, aldosterone showed no tendency to increase further (t paired data [20 vs. 40 min] $= 0.75$; $P > 0.5$). The regression relationship between the plasma aldosterone concentration at 20 min (x) and 40 min (y) showed a slope (1.03±0.07 SD) which did not differ significantly from 1.0 ($y = 1.03x + 0.89$; $r = 0.95$ $F = 192$; $P < 0.001$), despite a significant further increase in the angiotensin II concentration during the same interval ($y = 1.22x - 9.8$; $r = 0.97$; $P < 0.001$; slope SD $= 0.055$). It seems probable that the progressive small increase in the apparent arterial angiotensin II concentration reflected the gradual accumulation of angiotensin degradation products which have affinity for the angiotensin II antibody (7, 8, 10), but this was not assessed directly.

Responses in the subjects in whom a dose-response relationship was defined by infusing angiotensin II at 3 ng/kg/min for 20 min after a 20-min infusion at 1 ng/kg/min are listed in Table II. The responses to 3 ng/kg/min at 20 min did not differ significantly for all parameters from those found at the same dose when the infusion was initiated at that level. The results for the two doses in these individuals have, therefore, been pooled in the analyses. This approach will be useful in future studies by making it possible to define a dose-response relationship in individuals.

The relationship between angiotensin II concentration in all blood samples drawn before, and 20 mins or more after, the initiation of the angiotensin II infusion (when a new steady state for plasma aldosterone had been achieved) is shown in Fig. 3. A significant regression relationship was demonstrable between the angiotensin II (x) and aldosterone concentration (y) for both subjects in balance on a high salt intake ($r =$

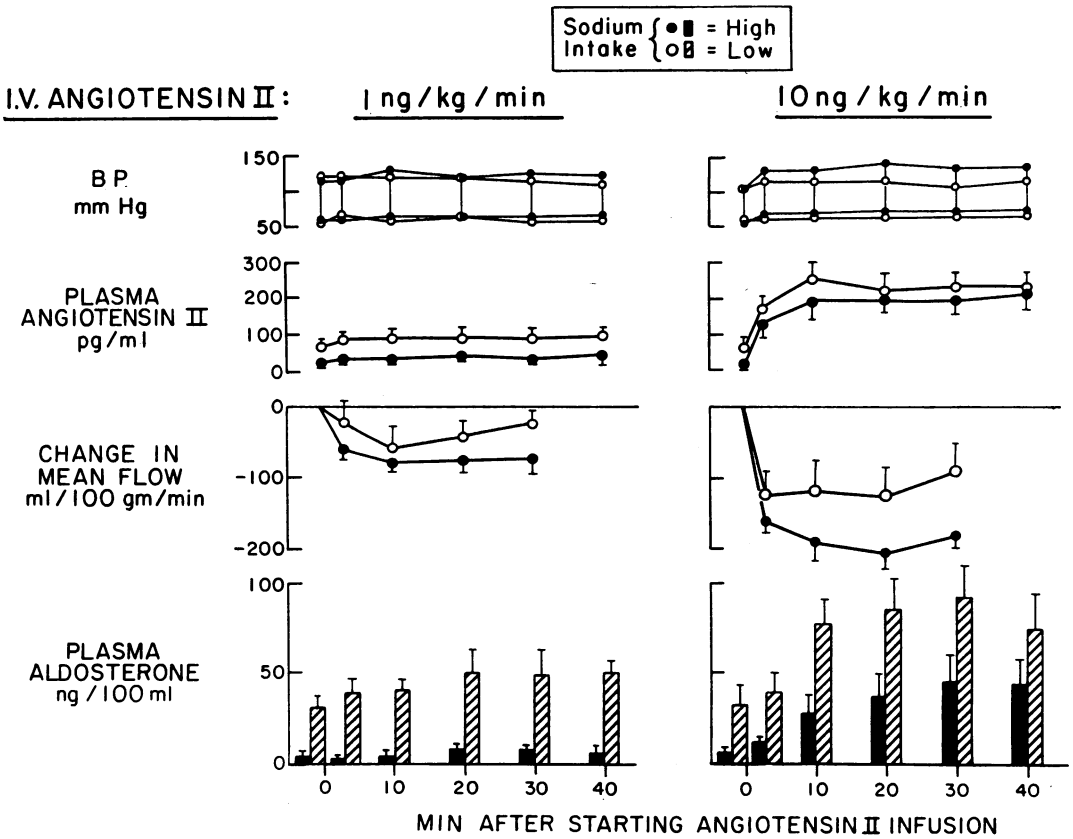

FIGURE 1 Time-course of the response to angiotensin II at the extreme doses used. The plasma angiotensin II concentration and blood pressure (BP) reach a new relatively stable level within 3 min; renal blood flow within 10 min; and plasma aldosterone within 20 min. Note the reciprocal influence of salt intake on the renal and adrenal response. Four subjects were studied at each dose on each diet.

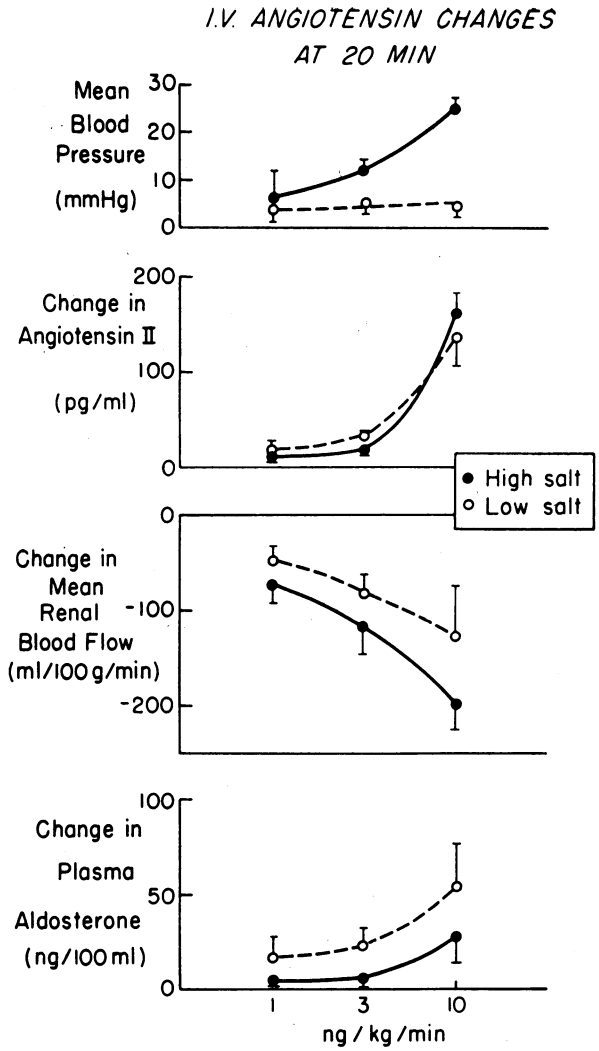

FIGURE 2 Dose-response relationships for the three angiotensin doses infused. All values are for the change documented at 20 min, the midpoint of the infusion. The change in the angiotensin II concentration was not significantly different in subjects on a high and low sodium intake. Significant differences between the two groups were demonstrable for plasma aldosterone ($P < 0.01$), the blood pressure ($P < 0.01$), and renal vascular ($P < 0.01$) response. 11 subjects on each diet were assessed with the 1 and 3 ng/kg/min doses, and 4 with the 10 ng/kg/min dose.

0.60; $P < 0.001$) and in the sodium-restricted subjects ($r = 0.69$; $P < 0.001$). The slope of the regression line in sodium-restricted subjects was 2.5-fold steeper than in the sodium-replete group, a highly significant increase ($t = 33.0$; $P < 0.0005$). Thus sodium restriction potentiated the adrenal response to angiotensin.

Serum cortisol in the entire group fell from 9.03±0.2 to 7.05±0.2 μg/100 ml during the angiotensin II infusion ($P < 0.01$). The values in subgroups who received graded infusions are listed in Table II. It is unlikely, therefore, that the aldosterone rise represented a response induced by ACTH.

In the two subjects in whom the procedure was performed without the infusion of angiotensin II, none of the physiological variables changed spontaneously by more than 10% during the procedure. Similarly, the intra-arterial infusion of angiotensin II in two subjects reduced renal blood flow but did not modify blood pressure, arterial angiotensin II, or aldosterone concentrations.

DISCUSSION

A reduction of salt intake is followed by a rapid decline of renal sodium excretion, establishing in 3–5 days a new state of balance in which sodium intake equals output. During the interval before balance is achieved in man about 150–200 meq of sodium, a small fraction of the normal total body stores, are generally excreted with sufficient water that plasma sodium concentration does not change. This modest reduction of the extracellular fluid volume has a profound influence on a number of systems: there is a striking increase in the rate of secretion and blood level of renin and in the concentration of circulating angiotensin II and aldosterone, and there is a reduction in renal blood flow (1–4). All of these responses are potentially relevant to the defense of extracellular fluid volume through sodium conservation. A substantial body of evidence suggests that the renal and adrenal responses are mediated, in part or in whole, by the increase in the renin and angiotensin levels. A major part of the difficulty in defining the influence of increased circulating angiotensin II, given the present potential for measuring its concentration adequately, has been related to a remarkable change in the response

TABLE II

Effect of Dietary Sodium on the Responses to Graded Infusions of Angiotensin II in Normal Subjects

Dose	Plasma		
	Angiotensin II	Aldosterone	Cortisol
ng/kg/min	*pg/ml*	*ng/100 ml*	*μg/100 ml*
10 meq sodium/100 meq potassium diet (n = 7)			
Control	47±6	18±1	10±4
1	60±8	25±3	7±3
3	85±8	38±2	10±3
200 meq sodium/100 meq potassium diet (n = 7)			
Control	24±2	6±1	10±5
1	34±4	10±1	9±4
3	57±6	13±2	8±3

Responses were determined at the end of a 20-min infusion of 1 ng/kg/min and again at the end of a 20-min infusion of 3 ng/kg/min (mean±SEM).

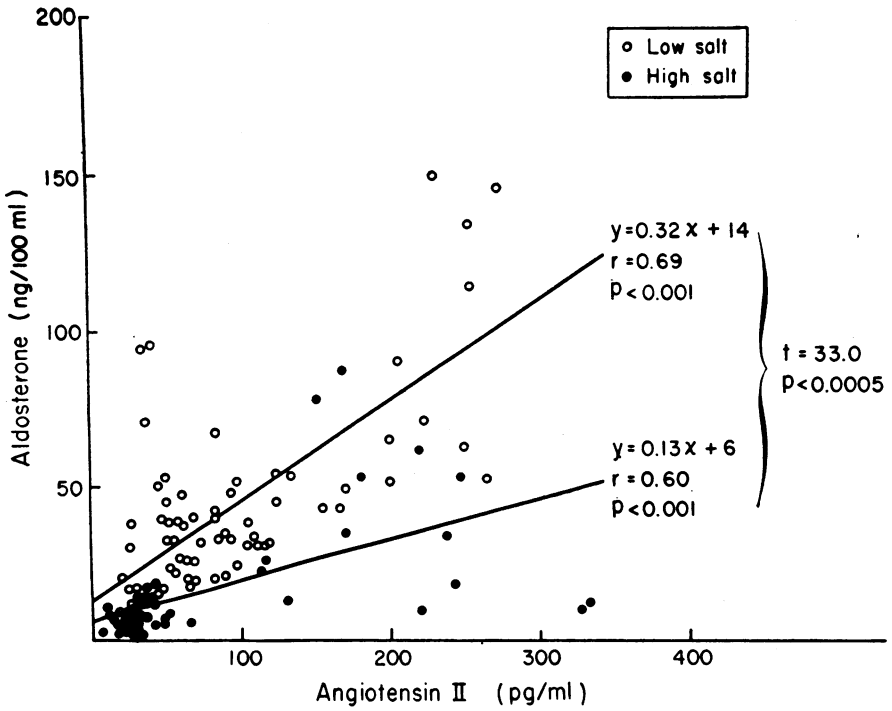

FIGURE 3 Regression relationships between plasma angiotensin and aldosterone concentrations in sodium-depleted and sodium-replete subjects. Both regression relationships are significant. Note the striking, highly significant ($P < 0.0005$) difference in the slopes of the two lines.

of effector system to angiotensin II when sodium intake is modified. The exploration of these relationships was the major thrust of this investigation.

Vascular sensitivity to angiotensin II falls significantly when sodium intake is restricted. While most frequently documented as a reduction in the pressor response (12–14), the reduction in sensitivity has also been defined in the vessels of the rabbit leg (15) and is especially marked in the case of the human kidney (4). It is even demonstrable in the rabbit aorta, where the implications for cardiovascular homeostasis must be minor (15). The reduced sensitivity thus may well reflect a universal characteristic of vascular smooth muscle. Brunner, Chang, Wallach, Sealey, and Laragh have suggested recently that this phenomenon reflects a reduced affinity of the vascular receptor for angiotensin II (16). A highly significant reduction in the renal vascular response to angiotensin II with sodium restriction has again been demonstrated in this study, although the difference between the responses in a low and high salt diet were considerably smaller than when the angiotensin was infused directly into the renal artery (4). Perhaps the direct effects on the renal vessels were offset, in part, by the pressor response that occurred with higher doses in the sodium-replete subjects. The role of angiotensin II in the renal blood flow reduction induced by sodium restriction has not been assessed directly in man, but it has been demonstrated recently that agents which block the conversion of angiotensin I to angiotensin II, or compete with angiotensin II for the receptor, induced a striking blood flow increase in dogs and rabbits on a low salt diet, an increase which did not occur when they were sodium replete (17, 18). Thus, despite the reduced renal vascular sensitivity to angiotensin II with salt restriction, it is likely that angiotensin II plays a role in the renal vascular response. A number of lines of evidence underline the importance of local renal vascular factors in sodium handling by the kidney (19–21). The renal vasoconstriction demonstrated with salt restriction in this and in many earlier studies is therefore immediately relevant to the overall problem of sodium homeostasis.

The adrenal's role in sodium homeostasis is unequivocal. There is also little debate about angiotensin's ability to increase aldosterone secretion (1–3). What has been the subject of recent debate is the primacy of angiotensin II as the mediator of the adrenal's response (2). A major line of evidence against a sole, or even dominant role of angiotensin II has been the failure of exogenous angiotensin, administered to sodium-replete man, to produce an adrenal response equivalent to that induced by sodium restriction (6, 22). Implicit in this

approach is the assumption that the restriction of salt intake does not modify the adrenal's responsiveness to angiotensin II.

In contrast to the broad agreement on the effect of salt restriction on vascular responses to angiotensin II, there has been considerable disagreement concerning the adrenal's responsiveness (3, 5, 6, 22–27) perhaps reflecting the greater difficulty of assessing this system. Ganong and Boryczka first demonstrated an enhanced adrenal response to angiotensin in the dog on a low salt diet (5); they further demonstrated that this alteration in sensitivity could be reproduced in sodium-replete dogs by the administration of homologous renin for 5 days (23). Davis, Burwell, and Bartter provided support for their observations in the dog by demonstrating a decreased sensitivity of the adrenal cortex to angiotensin II in the presence of a very high salt intake (24). Mixed evidence has been found in the rat (25, 26). In sheep, conversely, a reduced response of the adrenal cortex to angiotensin II occurred with sodium deficiency (3).

Several studies in man, immediately relevant to the assessment of the role of salt intake as a determinant of adrenal responsiveness to angiotensin, have been performed (6, 22, 27). In this study we have demonstrated an unequivocal sensitization of the adrenal's response to angiotensin II with sodium restriction in normal man. The increase in the circulating aldosterone concentration was larger at each dose of angiotensin II, despite an identical increase in the angiotensin II level in the subjects on a low salt diet. The possibility that this reflected not sensitization of the adrenal, but rather the fact that we were operating in a steeper portion of the angiotensin II-aldosterone relationship in these subjects, was ruled out by a second observation. Significant regression relationships were defined between arterial angiotensin II and aldosterone concentrations in both sodium-replete and sodium-depleted subjects over a wide and overlapping range of angiotensin II concentrations: the slope of the regression relationship was significantly steeper in the subjects in low salt balance. The results are not in accord with the conclusions of earlier studies, but examination of the other reports may account for the difference. Ames, Borkowski, Sicinski, and Laragh did not document an enhanced adrenal response with sodium restriction in normal subjects on a low salt diet when aldosterone secretion rate was used as the index of the adrenal response (27). In their study, the blood pressure increase was used to adjust the angiotensin dose; therefore a variable amount of angiotensin was infused. Also, the use of the aldosterone secretion rate as the index required a prolonged infusion, during which secondary responses may have occurred. In a more recent study, Boyd, Adamson, Arnold, James, and Peart defined the plasma aldosterone response to a fixed angiotensin II dose of 0.5 μg/min (22). They addressed themselves directly to the question of sodium intake's influence on the adrenal response and concluded that sensitization had not been demonstrated despite their findings: two of the four subjects showed a striking increase in sensitivity. Mendelsohn et al. were also unable to demonstrate altered sensitivity of the adrenal cortex with sodium restriction (6). They also used a fixed dose and studied a limited number of individuals. Perhaps because of the fixed dose and small number of subjects, the level of angiotensin II achieved with infusion was considerably lower in the sodium-restricted than in the sodium-loaded state, probably masking the sensitization. Moreover, the basal plasma angiotensin II level in that study did not change with sodium restriction: either they failed to achieve an effective low sodium balance, or a methodologic problem exists in their angiotensin II assay. In the present study and in most previous ones (22, 28–31), sodium restriction has produced a significant increase in the angiotensin II level.

An unequivocal increase in the aldosterone level was apparent within 10 min of initiating the angiotensin infusion, and a new plateau was achieved within 20 min in this study. While a significant correlation was found between the angiotensin II and aldosterone concentrations in arterial plasma, examination of Fig. 3 reveals considerable scatter about the regression lines. The variance is larger than the intrinsic error of the methods, suggesting that additional poorly defined factors also contribute to the relationship. A likely candidate is potassium balance (32). Despite our attempt to control potassium intake at an intermediate, 100 meq/day level, in fact considerable scatter in potassium excretion—and presumably in potassium intake—occurred. Clearly, this requires further investigation. The variability may account for a large part of the failure of the earlier studies to document the influence of sodium intake, because only four (22) and eight (6) subjects were studied, and the response was defined at only a single point in time. In this study, conversely, the relationships were defined on the basis of 87 determinations in 38 individuals. Given the intrinsic variability, it is easy to see how the relationships may have been obscured with a small number of observations.

Enhanced sensitivity of the glomerulosa cell to angiotensin II with sodium restriction is not a unique property. Previous studies have demonstrated a similar enhancement of the response to ACTH in normal man (33) and in the experimental animal (23). The rapidity of the response and information available from in vitro systems (34) suggests that sodium restriction

enhances the glomerulosa response through an increase in the activity of enzymes in the biosynthetic pathway.

The observations suggest that the increase in the angiotensin II blood level may itself sensitize the adrenal. Certainly, this is in accord with the earlier observation in the sodium-replete dog that repeated injections of renin sensitized as effectively as does sodium restriction (23).

In conclusion, sodium intake exerts a reciprocal influence on vascular and adrenal responses to angiotensin II. Restriction of sodium intake blunts vascular responses and potentiates those of the adrenal, a physiologically important influence in view of the aldosterone's role in sodium conservation. Moreover, the documentation of these basic relationships in normal man provides entrée to a more direct examination of their interaction in relevant disease states.

Note added in proof. Since this manuscript was accepted for publication a study has appeared (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.) which describes an essentially identical influence of salt intake on angiotensin II: aldosterone relationships in man.

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