The Adrenal Receptor for Angiotensin II is Altered in Essential Hypertension

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Research Article

To determine the mechanism underlying altered adrenal responsiveness in patients with essential hypertension, the renin-angiotensin-aldosterone axis was assessed in normotensive and hypertensive subjects using three pharmacological probes: SQ 20881, a converting enzyme inhibitor; saralasin, a competitive angiotensin antagonist with prominent agonist properties; and angiotensin itself. All subjects were studied while supine and in balance on a 10 meq Na/100 meq K intake. The decrement in plasma aldosterone with SQ 20881 in 26 hypertensive subjects (15±3 ng/dl) was normal (13±4 ng/dl), suggesting that the altered adrenal responsiveness in hypertensives is not because of a change in a postreceptor event or in the relative contribution of angiotensin to the control of aldosterone secretion.

Saralasin at a dose (0.1 μg/kg per min) that reduced aldosterone levels in all normals produced a normal aldosterone decrement (14±3 ng/dl) in 19 patients with renovascular hypertension (12±4 ng/dl). The same dose, however, had no net effect on plasma aldosterone levels in 70 patients with normal or high renin essential hypertension (−1±1 ng/dl) despite identical metabolic balance and control renin and angiotensin levels. The altered response could be explained by an agonist effect, aldosterone rising in 45 of the essential hypertensives. There were no significant differences between normal and abnormal responders in pre- and postcortisol, -potassium, -renin and -angiotensin concentrations.

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ABSTRACT To determine the mechanism under-
lying altered adrenal responsiveness in patients with
essential hypertension, the renin-angiotensin-aldo-
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tensive subjects using three pharmacological probes:
SQ 20881, a converting enzyme inhibitor; saralasin, a
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between normal and abnormal responders in pre- and
postcortisol, -potassium, -renin and -angiotensin con-
centrations.

Angiotensin was infused (0.1–3 ng/kg per min) in 15
patients with normal renin essential hypertension,
previously studied with saralasin. A probit transforma-
tion defined the dose required to induce a 50% increase
in aldosterone (ED50). In the patients in whom aldo-
sterone rose with saralasin, the dose required to induce

a 50% increase was significantly greater ($P < 0.001$)
than in those in whom aldosterone fell normally
(1.02±0.06 [SD] vs. 0.38±0.07 ng/kg per min). Vas-
cular responses were similar in the various groups. We
conclude that altered adrenal responsiveness to angio-
tensin in some essential hypertensive patients is
secondary to a change in the interaction of angiotensin
with its adrenal receptor.

INTRODUCTION

Recent studies have reported that adrenal responsive-
ness to angiotensin II (A II)[1] is altered (either increased
[1, 2] or decreased [3, 4]) in some patients with es-
sential hypertension. One possible explanation would
be a functional change in the relative importance of A II
in the control of aldosterone secretion or a change in the
activity of a postreceptor event.

Pharmacologic interruption of the renin-angiotensin
system has been useful in evaluating this system's role
in the control of arterial pressure (5, 6), aldosterone
secretion (7, 8), renal blood flow (9), and the develop-
ment or maintenance of hypertension (10, 11). In most
studies structural analogues of A II that are competitive
antagonists have been used. These analogues pre-
sumably bind to the A II receptor but fail to trigger
a response. In a few studies, the effect of blocking the
formation of A II (converting enzyme inhibition) has
been assessed.

The present study uses pharmacologic probes to
determine the most likely possibility for the altered
adrenal responsiveness in patients with essential
hypertension. Because the available blocking agents
are complicated, we felt it necessary to employ multiple
approaches. The first agent used was SQ 20881, a con-
verting enzyme inhibitor. This drug has no known

[1] *Abbreviations used in this paper*: A II, angiotensin II; PRA,
plasma renin activity.

direct effect on the adrenal, modifying adrenal secretion by reducing A II concentration (9, 14).

The second agent was saralasin (1-sar, 8-ala angiotensin II), a competitive antagonist of A II in some systems such as the rat adrenal in vitro and rabbit aorta (12, 13). Its action on the human adrenal is more complicated because it is a partial agonist (9), and under some conditions (high salt intake, low renin levels, etc.) it can stimulate rather than reduce adrenal secretion. Thus, four precautions were taken. The renin-angiotensin system was activated by sodium restriction; only subjects with normal or high renin levels were studied; the dose selected was that which only reduced aldosterone levels in normal subjects (14); and finally, in addition to studying patients with essential hypertension, patients with a secondary form of hypertension (renovascular) were also evaluated. In the renovascular patients, the pathogenesis of the hypertension and A II's role in it are better understood, thus providing an additional test of the capacity of saralasin to reveal angiotensin's action on the adrenal. Because altered adrenal responses were observed, a third probe — A II itself—was used to determine whether the alteration was related to a change in adrenal sensitivity to A II.

METHODS

Subjects

38 normotensive subjects (age range, 20–60 yr) and 104 hypertensive subjects (age range, 20–66 yr) who were studied at the Clinical Research Center of the Peter Bent Brigham Hospital, Boston, Mass. are the subject of this report. Responses in some of these normal subjects have been previously reported (14). The criteria for inclusion of hypertensive patients in the study were as follows: out-patient supine diastolic blood pressure >90 mm Hg mercury determined on three different occasions and documented evidence of hypertension for at least 6 mo before the study. All antihypertensive medications were discontinued at least 2 wk before admission. The subjects were fed an isocaloric 10 meq sodium/100 meq potassium diet. Daily 24-h urine samples were analyzed for sodium, potassium, and creatinine. Patients with primary aldosteronism, pheochromocytoma, and Cushing's syndrome were excluded by serum electrolytes, 24-h urinary vanillyl mandelic acid, metanephrines, 17-hydroxysteroid, and aldosterone levels. When clinically indicated, renal arteriogram and bilateral renal vein renin determinations were performed. 45% of the patients reported did have a renal angiogram. In 19 cases unilateral renal artery stenosis was documented. Of the rest, 20 patients had high renin essential hypertension. Patients with low renin essential hypertension were excluded. The normal plasma renin activity (PRA) in our laboratory is 2.4–15 ng/ml per h (upright posture, in balance on a 10 meq Na diet) (15). The protocol was approved by the Human Subjects Committee of the Peter Bent Brigham Hospital and written informed consent was obtained in all cases.

Protocols

Converting enzyme inhibition. In 15 normotensive patients and 26 patients with essential hypertension, adrenal responses to inhibition of A II generation was determined. Converting enzyme inhibition was accomplished by giving increasing doses of SQ 20881 (30–300 μg/kg) as intravenous boluses every 20 min until either a fall in diastolic pressure >9 mm Hg, a level greater than that observed in 95% of normal subjects, was produced or the maximum dose was reached. Basal plasma aldosterone, A II, cortisol, and potassium levels were determined and repeated 20 min after the last dose.

Saralasin infusion. In 23 normotensive controls, saralasin was infused at graded doses from 0.03 to 1.0 μg/kg per min (14). A dose of 0.1 μg/kg per min was selected to infuse into 19 patients with renovascular hypertension because it uniformly reduced aldosterone levels in normotensive subjects (14). Basal PRA, A II, aldosterone, cortisol, and potassium levels were determined and for the latter three repeated 20 min after starting the infusion. Then the saralasin infusion rate was increased at half log intervals every 6 min until a dose of 30 μg/kg per min to define the maximum decrement in arterial pressure. All subjects were studied supine after an overnight fast.

70 patients with essential hypertension were studied on an identical protocol. 50 patients had normal renin levels and the rest had elevated levels.

A II infusion. In 15 of the patients with normal renin essential hypertension who received saralasin, A II was infused on a different day. Again, all subjects were studied supine after an overnight fast in balance on a 10 meq Na/100 meq K intake. Control blood samples were obtained and a graded infusion of A II (Hypertensin-CIBA, Ciba-Geigy Corp., Summit, N. J.) was given with a Harvard Infusion Pump (Harvard Apparatus Co., Inc., Millis, Mass.) at rates of 0.1, 0.3, 1.0, and 3.0 μg/kg per min as previously described (1, 4). Each dose was infused for 30 min and blood samples were analyzed for A II, aldosterone, cortisol, sodium, and potassium. Blood pressure was monitored with an Arteriosonde (Hoffmann-La Roche, Inc., Nutley, N. J.) at 2-min intervals for a 20-min control period and throughout the angiotensin infusion.

Laboratory procedures

All blood samples were immediately spun and the plasma separated and frozen until time for assay. Samples for PRA and A II levels were drawn with EDTA as the anticoagulant; heparin was used as the anticoagulant in the samples for cortisol and aldosterone. Serum and urine sodium and potassium levels were measured by flame photometry with lithium as an internal standard. Plasma aldosterone, renin activity, and A II values were measured by radioimmunoassay techniques as previously described (16, 17). The values for renin activity and A II are reported in reference to the World Health Organization Standards 71-328 and 70-302, respectively. Therefore, the absolute values may differ somewhat from those reported previously from this laboratory. The results are expressed as mean±SEM. Statistical analyses for parametric data used Student's t test (18); for nonparametric data, Fisher Exact Test or chi-square test were used (19). Significant differences are $P < 0.05$ unless otherwise indicated.

RESULTS

Aldosterone response to converting enzyme inhibition. 15 normotensive and 26 essential hypertensive subjects were studied on this protocol. There were no significant differences between the two groups in age, sex, race, urine sodium, and potassium on the day

before study, or serum sodium, potassium and creatinine, and PRA, A II, aldosterone, and cortisol on the day of study. In the normotensive subjects, the decrement in aldosterone with SQ 20881 (13±3 ng/dl) was virtually identical to what had been previously reported with saralasin (14±3 ng/dl) (14). In the hypertensive subjects, both the mean decrement in aldosterone (15±3 ng/dl) and the slope of the regression line between pre- and postaldosterone levels (Fig. 1) were similar to the normotensive controls. The decrement in A II with converting enzyme inhibition in the hypertensive subjects (16±4 pg/ml) was also similar to that observed in the normotensive subjects (14±4 pg/ml).

Response of normotensive subjects and patients with renal vascular hypertension to saralasin. 23 normotensive subjects and 19 subjects with renovascular hypertension documented by angiography, renal vein renin lateralization, and significant improvement or cure after surgical correction received saralasin (0.1 μg/kg per min). There were no significant differences in age, sex, race, urine sodium, and potassium or serum sodium, potassium, or creatinine between the two groups. Their basal endocrine status were also similar, except the hypertensive patients had significantly greater (P < 0.02) basal PRA and A II levels than normotensive controls but similar potassium, aldo-
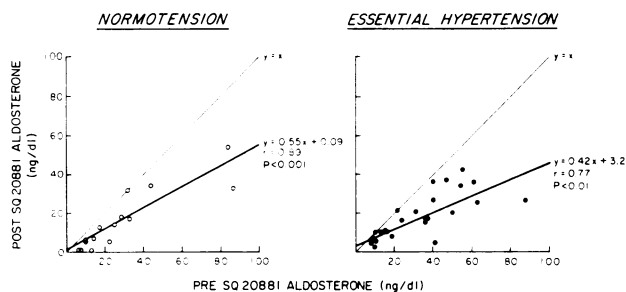

FIGURE 1   Regression relationship between control plasma aldosterone level and that observed 20 min after administering SQ 20881, a converting enzyme inhibitor, to 26 patients with essential hypertension and 15 normotensive controls. All subjects were studied supine and in balance on a low sodium intake.

sterone, and cortisol levels (Table I). Their aldosterone responses to saralasin were also identical to normal controls. The slope of the pre- and postsaralasin aldosterone regression line (0.479±0.014 [SD]; Fig. 2) was similar to that observed in normal controls (0.481 ±0.020) (Table I).

Response of patients with essential hypertension to saralasin infusion. There were no significant differences in age, sex, race, urine sodium, and potassium on

TABLE I

Biochemical and Physiological Characteristics of the Normotensive and Hypertensive
Subjects Infused with Saralasin

| | | Hypertensive subjects | |
	Normal subjects	Essential	Renovascular
Number	23	70	19
Age, yr	38±3	42±2	44±4
Serum creatinine, mg/dl	1.1±0.1	1.2±0.1	1.1±0.1
Sodium, meq/liter	140±1	144±1	142±1
Potassium, meq/liter	4.2±0.1	4.3±0.1	4.1±0.1
Urine sodium, meq/day	12±3	10±1	14±3
Potassium, meq/day	88±4	79±3	88±6
Diastolic blood pressure, mm Hg			
Control	72±3	87±2*	100±3*
Delta with saralasin, maximum			
with dose of 30 μg/kg/min	-1.5±1.2	-1.7±1.1	-14.6±3.2*
PRA, ng/ml/h			
Control	3.9±0.4	6.3±0.6*	10.2±2.2*
Plasma A II, pg/ml			
Control	55±4	60±4	113±29*
Plasma aldosterone, ng/dl			
Control	25±3	21±2	30±6
Delta with saralasin, 0.1 μg/kg/min	-14±3	-1±1*	-12±4
Slope of regression line, pre vs. post	0.481±0.02 (SD)	0.609±0.011*	0.479±0.014
Plasma cortisol, μg/dl			
Control	14±2	11±1	12±2
Delta with saralasin, 0.1 μg/kg/min	1±2	-2±1	-1±1

All values are means±SEM.
* P < 0.02 significantly different than normal subjects.
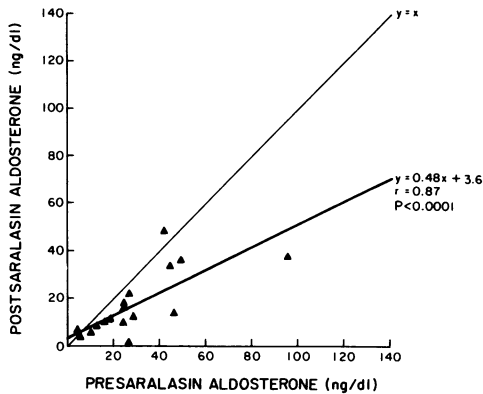
FIGURE 2 Regression relationship between control plasma aldosterone level and that observed 20 min after administering 0.1 μg/kg per min of saralasin. All 19 patients had renovascular hypertension and were studied supine on a low sodium intake.

the day before study, or serum sodium, potassium and creatinine and plasma cortisol and aldosterone on the day of the study between the normal subjects and the patients with essential hypertension (Table I). There were also no significant differences between changes in cortisol or potassium during the study. Diastolic arterial pressure was significantly greater ($P < 0.01$) in the
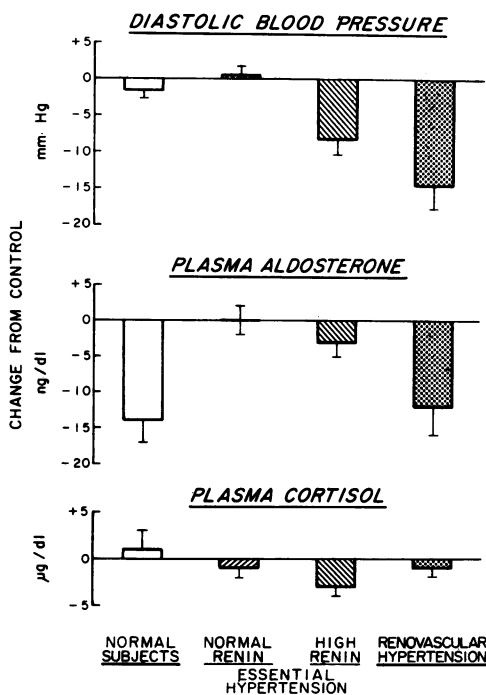

FIGURE 3 Comparison of vascular and adrenal responses to saralasin in normal and hypertensive subjects. All studies were performed supine in balance on a low sodium intake. The adrenal response was that observed at a dose of 0.1 μg/kg per min, whereas the vascular response was the maximum observed giving as much as 30 μg/kg per min (Mean±SEM).

hypertensive patients but the maximum change in pressure with comparable amounts of saralasin was not significantly different from the control subjects (Table I and Fig. 3). The hypertensive patients had greater renin levels ($P < 0.02$), as anticipated, because high renin subjects were included but the levels were less ($P < 0.02$) than in the renovascular patients with hypertension.

There were, however, two striking differences between the patients with essential hypertension and those with renovascular disease or normotensive controls. First, the decrement in aldosterone was significantly less ($P < 0.01$; Fig. 3), and second, the slope of the regression line between the pre- and postaldosterone levels was significantly greater ($P < 0.001$) in the essential hypertensive patients (0.61±0.01 [SD]) (Fig. 4; Table I). This difference can be explained by an increase in aldosterone levels after saralasin in nearly half the essential hypertensive subjects (aldosterone-increment group; Fig. 4). In contrast, no sodium-restricted, normotensive subjects (14) and only 1 out of 19 renovascular patients had an increase in aldosterone after administration of this dose (0.1 μg/ kg per min) of saralasin. Whether the hypertensive patients had high or normal renin levels made little difference; both were significantly different from the normotensive controls but not from each other in terms of adrenal response (Fig. 3). Furthermore, in contrast to the normotensive subjects, where responses to saralasin and converting enzyme inhibition were similar, in the patients with essential hypertension the decrement in aldosterone with SQ 20881 (15±3 ng/dl) was significantly greater ($P < 0.001$) than with saralasin (1±1 ng/dl) (Fig. 5). There were no significant differences either between the cumulative sodium deficit or the number of days necessary to achieve low salt balance in the two groups of essential hypertensive patients. Those in the aldosterone-increment group lost 78±11 meq sodium and took 3.5±0.3 d to achieve low salt balance, whereas in the aldosterone-decrement group 77±13 meq of sodium was lost and 3.4±0.3 d were necessary.

Response to angiotensin infusion. A comparison of a number of parameters in those patients with normal renin essential hypertension whose aldosterone levels increased with saralasin (aldosterone increment group) and those whose aldosterone levels decreased (aldosterone-decrement group), and in normotensive controls revealed only one significant difference (Table II): the basal aldosterone level was significantly lower ($P < 0.005$) in the aldosterone-increment group than in the other two groups. The similar A II levels in the three groups suggest the adrenal is less sensitive to A II in those patients with altered adrenal responses to saralasin. This was assessed directly in eight aldosterone-decrement and seven aldosterone-increment
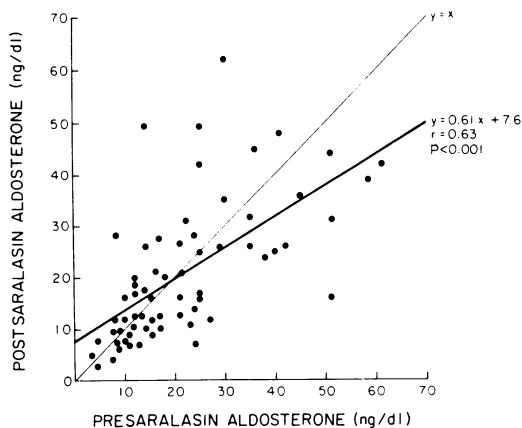
FIGURE 4 Regression relationship between control plasma aldosterone level and that observed 20 min after administering 0.1 μg/kg per min of saralasin. All 70 patients had essential hypertension and were studied supine on a low sodium intake.

patients selected so their control aldosterone levels were similar (Fig. 6). A probit transformation was used to define the angiotensin dose required to induce a 50% increase in plasma aldosterone concentration (ED_{50}) and its SD (20). From the probit transformation data, the ED_{50} in the aldosterone-increment group (1.02 ±0.06 [SD] ng/kg per min) was significantly greater ($P < 0.001$) than in the aldosterone-decrement group (0.38±0.07 [SD] ng/kg per min). Thus, the adrenal in patients in whom an aldosterone increment occurred in response to saralasin were less sensitive to A II. In contrast, vascular responses were similar in the two groups in agreement with an earlier study (4).

DISCUSSION

Although many investigators have documented derangements in renin release in essential hypertension, only recently has an alteration in aldosterone secretion independent of renin abnormalities been suggested. Streeten et al. (21) were the first to report this alteration, noting that half their patients with normal renin essential hypertension had subnormal secretory responses to chronic volume depletion (sodium restriction). Since their studies, a dissociation between renin and aldosterone response to acute volume depletion (either venous hemorrhage or diuretic-induced) (3, 22–24) and a decreased adrenal response to infused A II (4) have also been reported. On the other hand, Kisch et al. (1) and Wisgerhof and Brown (2) have suggested that some essential hypertensive patients, particularly those with low plasma renin levels, may have an increased adrenal responsiveness to A II. Thus, individuals with normal renin essential hypertension have been reported to have either an increased or a decreased adrenal responsiveness to A II when compared

to normal subjects. This apparent discrepancy is probably related to the diet on which the studies were conducted. In normotensive subjects, adrenal responsiveness to A II is significantly modified by dietary sodium intake with threefold enhancement if sodium intake is decreased from 200 to 10 meq/day (25, 26). An increased adrenal responsiveness in patients with hypertension has only been documented under conditions of high sodium intake and a decreased responsiveness only when sodium intake is restricted, suggesting that the sodium-dependent swing in adrenal A II responsiveness in these patients is smaller than normal. Possible mechanisms to explain this altered adrenal responsiveness include: (a) a change in the relative contribution of A II compared to other factors (potassium, ACTH, etc.) to the control of aldosterone; (b) a change in the interaction of A II with its adrenal receptor; or (c) a change in a postreceptor event. The present study used three pharmacological probes to assess the relative importance of these mechanisms.

SQ 20881 (pry-try-pro-arg-pro-gln-ile-pro-pro) is a peptidyl-dipeptide hydrolase inhibitor that reduces the conversion of angiotensin I into A II. It also inhibits the inactivation of bradykinin, a potent vasodilator, thus, complicating the interpretation of its effect on arterial pressure (5, 27). However, neither SQ 20881 nor brady-
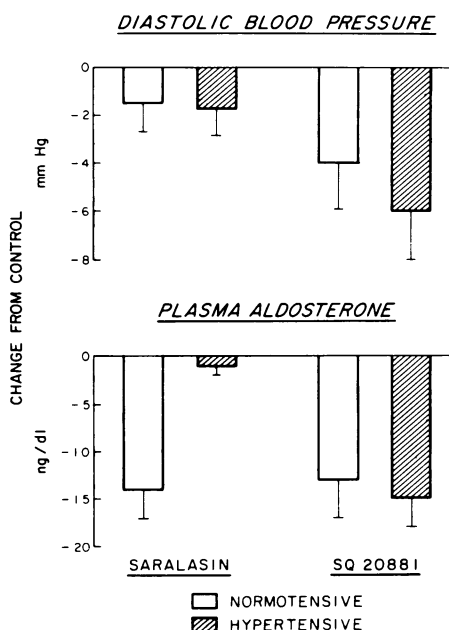

FIGURE 5 Comparison of vascular and adrenal responses to converting enzyme inhibition (SQ 20881) and angiotensin blockade (saralasin) in normotensive and hypertensive subjects. Doses used are as defined in the text and Fig. 3. All subjects were studied supine, in balance, on a low sodium intake. Plasma aldosterone responses were similar except in hypertensive subjects given saralasin. Vascular responses were similar in both groups (Mean±SEM).
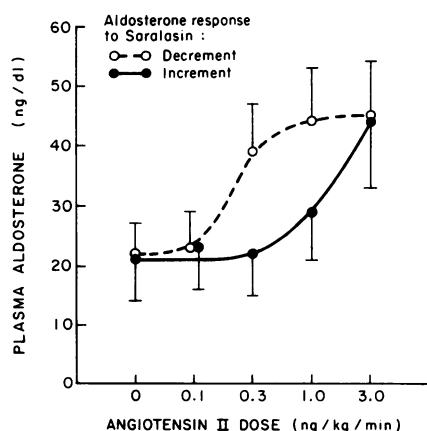
TABLE II
Comparison of Biochemical Characteristics of Patients with Normal Renin
Essential Hypertension Who had a Rise in Aldosterone with
Saralasin with Those Who had a Fall

| | | Essential hypertension | |
	Normal subjects	Aldosterone increment	Aldosterone decrement
Number	23	29	21
Control			
Plasma angiotensin II, *pg/ml*	55±4	52±5	60±8
Plasma aldosterone, *ng/dl*	25±3	16±2*	27±3
Plasma cortisol, *μg/dl*	14±2	11±1	10±1
Serum potassium, *meq/liter*	4.2±0.1	4.3±0.1	4.2±0.1
Diastolic blood pressure, *mm Hg*	72±3	88±3	85±2
Delta with saralasin			
Plasma aldosterone, *ng/dl*	−14±3	8±2*	−10±2
Plasma cortisol, *μg/dl*	1±2	−2±1	−1±1
Serum potassium, *meq/liter*	0.0±0.1	0.1±0.1	0.0±0.1
Diastolic blood pressure, *mm Hg*	−1.5±1.2	0.2±1.3	−3.8±1.8

Endocrine responses were measured after a dose of 0.1 $\mu g/kg$ per min. Vascular response was maximum achieved with a dose between 0.1 and 30 $\mu g/kg$ per min. All values are means±SEM.
* $P < 0.02$ significantly different from normal subjects.

kinin have a known direct effect on aldosterone secretion. Thus, adrenal responses to this drug are probably secondary to the previously documented (8, 28) change in A II concentration. Normotensive and hypertensive patients had virtually identical adrenal responses to this drug. In all subjects on the low salt diet, the aldosterone levels fell with the extent of decline related to the basal aldosterone concentration but not to the presence of hypertension (Fig. 1). These

FIGURE 6 Dose-response relationships between A II and plasma aldosterone in eight patients with normal renin essential hypertension who had a decrement in aldosterone with saralasin, and seven who had an increment. All subjects were studied supine in balance on a low sodium intake (Mean ±SEM).

results imply that A II's contribution to the control of aldosterone secretion in the hypertensive patient is normal.

Saralasin is a partial agonist in some systems including the human adrenal (9), and therefore, using it to define A II's action on the adrenal is complicated. The adrenal response to saralasin is critically dependent on the status of sodium balance and presumably to the level of endogenous, circulating A II. In normal subjects with low circulating levels of A II because of a high sodium intake the agonist response to saralasin predominates, with a rise in aldosterone (9). On the other hand, on a low sodium diet, saralasin reduces aldosterone levels as its antagonist properties predominate (14). Because saralasin completely inhibits adrenal responses to infused A II in normal subjects on a high sodium intake (9), it is likely that the critical factor determining whether under normal conditions saralasin produces a rise (agonist effect) or fall (antagonist effect) in aldosterone secretion is dependent on the circulating A II levels. Furthermore, as would be anticipated of a partial agonist, saralasin's inhibitory effect, even in the presence of high circulating levels of A II, is dose dependent. This latter influence was minimized by defining the dose-response relationship between saralasin and aldosterone. An infusion rate of 0.1 $\mu g/kg$ per min always reduced aldosterone levels in sodium-restricted normal subjects (14). However, increasing the infusion rate 10-fold to 1 $\mu g/kg$ per min produced a rise in plasma aldosterone levels in 20% of the subjects (14). The similar decrements in plasma

aldosterone in normal subjects with the optimum dose of saralasin and with SQ 20881 suggest that saralasin's partial agonist property did not obscure the normal adrenal response to the reduction in A II levels previously raised by sodium restriction (Fig. 5).

As a second test of the utility of saralasin in defining A II's action on the adrenal in essential hypertension, we assessed its effect in renovascular hypertension where the pathogenesis of the secondary aldosteronism is reasonably well understood. The adrenal's response to 0.1 μg/kg per min of saralasin was identical to that in normotensive subjects. Thus, in both sodium-restricted normal subjects and in sodium-restricted patients with one type of hypertension in which A II clearly plays an important role, saralasin uncovered a normal contribution of A II to aldosterone secretion.

In patients with normal or high renin essential hypertension, on the other hand, a more complicated response to saralasin was found. Some responded normally, whereas in others (nearly one-half) saralasin induced a rise in aldosterone (aldosterone-increment group), even though they were in low salt balance (Table I) and received saralasin at a rate that only reduced aldosterone levels in normal subjects and patients with renovascular hypertension. Furthermore, none had low renin hypertension. It is unlikely that a change in other parameters, e.g., ACTH or potassium, known to independently modulate aldosterone secretion could account for the altered responsiveness because basal cortisol and potassium levels, potassium balance and changes in potassium and cortisol levels during the acute studies were similar in the various groups (Table II). A change in aldosterone metabolism in the aldosterone-increment group could have occurred and was not specifically assessed. However, the changes in responsiveness to saralasin and A II were specific for the adrenal because vascular responses were similar in the various groups. Thus, an alteration in aldosterone metabolism because of a difference in the response of hepatic or renal blood flow to these agents seems unlikely. Although a recent report of adrenal responses to saralasin in hypertension by Brown et al. (29) seems to be in agreement with the present study, other factors could explain their results. For example, they used a saralasin dose 20-fold greater (≅20 μg/kg per min) than that producing a variable adrenal response even in normotensive subjects (14). Second, their hypertensive subjects with an agonist response to saralasin had low PRA and, presumably, A II levels. Even normal subjects with low PRA levels have an agonist response to this agent (9).

One mechanism for the rise in aldosterone with saralasin could have been an enhanced adrenal sensitivity to A II. Although most reports of this phenomenon have been in low renin patients (2), some subjects have had normal renin hypertension (1). This pos-

sibility seemed unlikely because the basal aldosterone levels in the aldosterone-increment group were lower than in the aldosterone-decrement group with similar A II levels suggesting, if anything, a decreased adrenal sensitivity. This was directly assessed by infusing A II and measuring the adrenal's response. The adrenal in patients with an agonist response to saralasin was also less sensitive to exogenous A II (Fig. 6).

The mechanism of the altered adrenal responses to A II and saralasin in the sodium-restricted patients with essential hypertension is unclear. A change in the contribution of A II to the control of aldosterone in these patients is made unlikely by the response to SQ 20881, although a direct comparison of the adrenal's response to converting enzyme inhibition and saralasin in the same hypertensive patients has not been reported. The same data also makes a change in the activity of an intracellular step—a post A II receptor event—unlikely, supporting the observations that adrenal responses to ACTH have been normal in essential hypertension (3, 30). More rigorous studies comparing the dose-response relationships to A II, ACTH, and potassium in the same individuals, however, are still needed. The present results are best accounted for on the basis of a change in the interaction of A II with its adrenal receptor. For example, Hauger et al. have suggested that angiotensin administration in rats increases the number of A II binding sites (31). If correct, then one possible explanation for our results is a relative failure of A II in the aldosterone-increment group to regulate (increase) its own adrenal receptors in response to sodium restriction, a high A II state. Although an alteration in the number of receptors could account for the change in adrenal sensitivity to A II, it could not account for the modification in its response to saralasin. Thus, a more plausible theory would be that there is a change in the structure of the adrenal A II receptor in the aldosterone-increment group so that it responds better to the altered A II molecule, saralasin, than to A II itself. This change produces a condition where the adrenal's response to saralasin and A II in the sodium-restricted, hypertensive subjects is similar to that observed in sodium-loaded normal subjects, i.e., an agonist response to saralasin and a decreased sensitivity to A II (9, 25, 26). Therefore, even though dietary sodium intake, state of external sodium balance, and circulating A II levels in the aldosterone-increment hypertensive group were the same as that of the normal subjects on a low sodium intake, their adrenals responded as if they were ingesting a high sodium diet. Thus, despite an identical state of low sodium balance in the aldosterone-increment, hypertensive group, their adrenals apparently perceive an expanded extracellular space. Such an abnormality provides further support to the thesis that the sodium-dependent swing in adrenal A II responsiveness is smaller in these patients. This alteration could

produce hypertension in several ways. In a sodium-depleted state it would necessitate greater activation of the renin-angiotensin system to close the volume-renin-aldosterone feedback loop, potentially resulting in greater vasoconstrictor activity. On the other hand, in the sodium-repleted state inappropriate volume expansion may result because of the enhanced adrenal response to A II. Critical assessment of this hypothesis, however, will require the development of more specific pharmacologic probes.

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