Responsiveness of Plasma 18-Hydroxycorticosterone and Aldosterone to Angiotensin II or Corticotropin in Nonazotemic Diabetes Mellitus

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SUMMARY

To assess the function of the final step of the pathway for aldosterone biosynthesis, the responsiveness of plasma 18-hydroxycorticosterone and aldosterone concentrations to angiotensin II infusion was studied in 14 patients with nonazotemic diabetes mellitus as compared with 14 normal controls approximately matched for sex and age. In addition, the responses of both steroids to corticotropin injection were investigated in the diabetic patients. Under basal conditions, plasma aldosterone levels were slightly lower in the patients than in normal controls, while plasma 18-hydroxycorticosterone concentrations were similar in the two study groups. Angiotensin II induced marked and comparable increases in plasma 18-hydroxycorticosterone and aldosterone levels in normal and diabetic subjects. Plasma 18-hydroxycorticosterone and aldosterone levels before and after angiotensin II infusion were significantly interrelated; this correlation was similar in normal subjects ($r = 0.61$; $P < 0.001$) and diabetic patients ($r = 0.52$; $P < 0.005$). Plasma 18-hydroxycorticosterone and aldosterone were significantly increased by corticotropin in the patients. These findings indicate that the terminal step of aldosterone biosynthesis, which involves the production of 18-hydroxycorticosterone and aldosterone, is largely unaltered in patients with nonazotemic diabetes mellitus. DIABETES *32*:1–5, January 1983.

Uncomplicated diabetes mellitus is frequently associated with a blunted responsiveness of plasma aldosterone to postural change, which may be partly explained by concomitant renin deficiency.[1,2] However, there is a dissociation between the responses of plasma aldosterone and renin activity to upright posture in certain diabetic patients,[1,3] which raises the possibility that some additional abnormality of aldosterone control is present. One possibility is that a biosynthetic defect of adrenal function may exist; evidence for a defective conversion of 18-hydroxycorticosterone to aldosterone has been noted in seven diabetic patients with hypoaldosteronism.[4–7] Whether and to what extent such an enzyme deficiency is present in patients with uncomplicated diabetes mellitus and if it may account for aldosterone hyporesponsiveness has been unknown. The present investigation was undertaken to assess the function of the final step of the aldosterone biosynthetic pathway in patients with stable, nonazotemic diabetes mellitus.

SUBJECTS AND METHODS

Fourteen normal volunteers and 14 patients with diabetes mellitus were studied. The normal subjects included nine males and five females, ranging in age from 28 to 60 yr [mean, 50 ± 3 (SEM) yr]. The normal volunteers had a normal fasting plasma glucose and a blood pressure consistently below 140/90 mm Hg. The diabetic patients included 10 males and 4 females, ranging in age from 28 to 68 yr (mean, 50 ± 4 yr). Diabetes mellitus was established by standard laboratory methods; the known duration of diabetes ranged from 4 to 20 yr, averaging 12 ± 2 yr. Two patients were treated by diet, one by diet and oral hypoglycemic agents, and 10 by diet and insulin. Diabetic retinopathy, as evidenced by retinal microaneurysms, was present in six patients; polyneuropathy, as evidenced by diminished sensation of vibration in the lower limbs, in six; nephropathy, as evidenced by proteinuria (0.3–1.5 g/24 h), in two; and no diabetic complications could be demonstrated in eight. Twelve patients had a blood pressure consistently below 140/90 mm Hg; two had mild hypertension (supine blood pressure 151/85 and 122/92 mm Hg, respectively). None of the patients had congestive heart failure, angina, arrythmia, edema, or renal failure (plasma creatinine >1.5 mg/dl); their metabolic state was stable and fairly well controlled.

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Received for publication 4 May 1982 and in revised form 12 August 1982.

To avoid very high or low sodium intakes, we instructed all subjects to adhere to their usual diet but not to add salt to their food, starting at least 5 days before the study.[8] In the hypertensive patients antihypertensive drugs were discontinued 4 wk before the study. The dose of insulin or hypoglycemic agents and carbohydrate intake were not altered. The following investigations were performed on 3 different days during a 7-day period.

(1) Twenty-four-hour urinary sodium, potassium, norepinephrine and epinephrine excretion rates, exchangeable sodium, and blood volume were determined; blood pressure, heart rate, plasma sodium, potassium, creatinine, glucose, renin activity, aldosterone (A), norepinephrine, and epinephrine were measured between 8 and 9 a.m. after 1 h of recumbency according to our standard procedure.[1] Blood pressure, heart rate, plasma renin activity, A, norepinephrine, and epinephrine were again determined after 1 h of ambulation.

(2) In both normal and diabetic subjects, the effects of angiotensin II (AII) on plasma 18-hydroxycorticosterone (18-OH-B) and A were assessed. According to our standard procedure,[2,9] basal blood pressure, heart rate, plasma 18-OH-B, A, and cortisol levels were determined after a 60-min equilibration period. AII (Hypertensin) was then infused, and the dose rate was titrated to reach two target levels of diastolic blood pressure, namely 10–15 (step 1) and 15–25 (step 2) mm Hg, respectively, above the basal diastolic blood pressure. Blood samples were obtained after 15–20 min of infusion at these two rates for determination of 18-OH-B and cortisol levels; at the higher dose, plasma A was also measured.

(3) The effects of corticotropin on plasma 18-OH-B and A were studied in 13 of the diabetic patients (mean age, 51 ± 4 yr). Plasma sodium, potassium, renin activity, 18-OH-B, A, and cortisol were determined after 1 h of recumbency. These basal blood samples were drawn between 8 and 9 a.m. Alpha-$^{1-24}$corticotropin (0.25 mg, Cortrosyn) was then injected intravenously and plasma 18-OH-B, A, and cortisol were again determined 30 and 60 min thereafter.[10]

Blood pressure was measured using a standard sphygmomanometer; each recorded pressure was the mean of three measurements. For the AII infusion test, blood pressure was recorded using an automatic recorder (Physiometrics SR 2); plasma and urinary sodium and potassium concentrations were determined by flame photometer; creatinine, by autoanalyzer; glucose, by the hexokinase method; blood volume and exchangeable sodium, by a standard isotope dilution technique using ^{125}I-human serum albumin and ^{24}Na.[11] Plasma renin activity and aldosterone were measured by radioimmunoassay.[12,13] 18-OH-B concentration was measured by radioimmunoassay after preliminary purification by layer chromatography.[14] Plasma cortisol was measured by competitive protein binding assay;[15] norepinephrine and epinephrine were measured in the urine with a fluorometric[16] and in plasma by a radioenzymatic method.[17]

For statistical analysis, the natural logarithm transformation of plasma renin activity, 18-OH-B, A, norepinephrine, and epinephrine was used. Statistical analysis included Student's paired or unpaired two-tailed *t* test and analysis of variance or covariance.

RESULTS

Basal clinical and biochemical findings. The normal subjects and the diabetics did not differ significantly in mean age, body weight, blood pressure, and heart rate, as well as in the other considered blood pressure-regulating factors (Table 1), except for an increase in exchangeable body sodium ($P < 0.05$) and a decrease in the supine and upright plasma epinephrine levels ($P < 0.05$) in the latter. All parameters did not differ between diabetic subgroups with or without diabetic complications (Table 1).

Effects of angiotensin II. The preinfusion plasma levels of renin, 18-OH-B, and cortisol were comparable between normal and diabetic subjects, but the basal plasma A concentration was on average lower in the latter ($P < 0.025$) (Table 2). The ratio of 18-OH-B to A averaged 2.5 ± 0.8 in normal subjects and 3.7 ± 0.8 in the diabetic patients (difference statistically not significant).

The AII dose rates required to elevate the diastolic blood pressure to the two defined target levels (steps 1 and 2, see SUBJECTS AND METHODS) were comparable in normal and diabetic subjects (Table 2). AII markedly increased the plasma levels of 18-OH-B and A; percentile increases did not differ between the two study groups. Plasma levels of 18-OH-B measured before and after AII infusion correlated positively with the concomitant plasma A concentrations; this correlation did not differ between normal and diabetic subjects (Figure 1). The ratio of 18-OH-B to A was significantly ($P < 0.025$) decreased in normal subjects (from 2.5 ± 0.8 to 1.0 ± 0.1) after AII; but a similar tendency in the patients (from 3.7 ± 0.8 to 2.0 ± 0.5) did not reach statistical significance.

Preinfusion values of blood pressure, plasma renin activity, cortisol, 18-OH-B, and A and the AII-induced changes in blood pressure, 18-OH-B, and A levels did not differ between diabetics with or without complications.

Effects of corticotropin. Before the i.v. injection of alpha-$^{1-24}$corticotropin, plasma sodium averaged 137.2 ± 0.3 mmol/L; plasma potassium, 4.07 ± 0.07 mmol/L; renin activity, 1.65 ± 0.46 ng/ml/h; cortisol, 10.0 ± 0.9 μg/dl; 18-OH-B, 6.1 ± 0.8 ng/dl; and A, 2.7 ± 0.6 ng/dl. In these diabetics, the ratio of plasma levels of 18-OH-B to A averaged 2.9 ± 0.5. After administration of corticotropin, mean plasma cortisol increased to 23.6 ± 1.1 μg/dl at 30 min ($P < 0.001$) and to 27.2 ± 1.4 μg/dl at 60 min. Plasma 18-OH-B and A were markedly increased at 30 min after corticotropin (to 26.6 ± 2.7 ng/dl and 16.3 ± 1.6 ng/dl, respectively; $P < 0.001$) and not further modified at 60 min (23.6 ± 2.3 and 14.8 ± 2.2 ng/dl). The ratio of 18-OH-B to A was slightly, not significantly, decreased after corticotropin (1.9 ± 0.3 at 30 min and 2.0 ± 0.2 at 60 min). Corticotropin-induced increments in plasma 18-OH-B or A did not differ between diabetics with or without complications.

DISCUSSION

The findings of the present study indicate that the terminal steps of A biosynthesis are probably largely unaltered in patients with nonazotemic diabetes mellitus who do not display the syndrome of hyporeninemic hypoaldosteronism.[18] This conclusion is supported by the observation of (1) similar increases in both plasma 18-OH-B and A in response to AII

TABLE 1
Clinical and biochemical findings under basal conditions in normal and diabetic subjects (mean ± SEM)

		Diabetic patients		
	Normal subjects	All	Without complications	With complications
N	14	14	8	6
Age (yr)	50 ± 3	50 ± 4	45 ± 5	57 ± 4
Body weight (kg)	75.7 ± 2.6	73.9 ± 4.9	71.6 ± 4.9	77.1 ± 9.8
Blood pressure (mm Hg)				
Supine	124/81 ± 2/2	120/73 ± 4/4	123/76 ± 5/3	117/70 ± 4/4
Upright	106/82 ± 3/1	119/82 ± 4/2	123/82 ± 3/2	114/81 ± 6/6
Heart rate (beats/min)				
Supine	63 ± 2	70 ± 3	68 ± 4	73 ± 6
Upright	89 ± 4	93 ± 4	91 ± 5	98 ± 9
Exchangeable sodium (%)*	100.4 ± 2.6	108.4 ± 2.5†	104.2 ± 2.7	113.3 ± 4.7†
Blood volume (%)*	107.7 ± 4.0	103.5 ± 3.2	105.2 ± 1.8	101.1 ± 7.4
Plasma sodium (mmol/L)	138.7 ± 0.7	137.3 ± 1.2	138.2 ± 2.0	136.2 ± 0.8
Plasma potassium (mmol/L)	4.26 ± 0.09	4.26 ± 0.13	4.07 ± 0.16	4.49 ± 0.23
Plasma creatinine (mg/dl)	1.05 ± 0.04	0.99 ± 0.05	0.97 ± 0.05	1.01 ± 0.09
Plasma glucose (mg/dl)	—	222 ± 28	192 ± 36	259 ± 43
Plasma renin activity (ng/ml/h)				
Supine	1.24 ± 0.18	1.55 ± 0.27	1.30 ± 0.22	1.89 ± 0.47
Upright	3.37 ± 1.07	2.79 ± 0.41	2.55 ± 0.57	3.12 ± 0.60
Plasma aldosterone (ng/dl)				
Supine	5.5 ± 1.1	2.7 ± 0.6	1.4 ± 0.3	4.3 ± 0.9
Upright	21.4 ± 5.5	9.6 ± 1.6	6.6 ± 1.6	14.7 ± 1.6
Plasma norepinephrine (ng/dl)				
Supine	24.1 ± 3.2	18.6 ± 2.6	17.2 ± 3.4	20.3 ± 3.1
Upright	55.0 ± 5.5	45.9 ± 6.2	43.7 ± 9.6	48.9 ± 7.9
Plasma epinephrine (ng/dl)				
Supine	4.1 ± 0.5	1.9 ± 0.3‡	2.0 ± 0.3†	1.9 ± 0.74†
Upright	6.8 ± 1.2	3.3 ± 0.4†	3.5 ± 0.7	3.0 ± 0.5
Urinary sodium (mmol/24 h)	141 ± 11	183 ± 21	179 ± 29	191 ± 31
Urinary potassium (mmol/24 h)	72 ± 7	75 ± 10	65 ± 13	88 ± 14
Urinary norepinephrine (μg/g creat)	24.4 ± 2.8	23.7 ± 2.9	22.6 ± 3.4	25.2 ± 5.4
Urinary epinephrine (μg/g creat)	3.5 ± 0.8	3.0 ± 0.8	4.0 ± 1.1	1.7 ± 0.8

*Percentage of the value expected for normal subjects of the same sex and body surface area.[21]
†$P < 0.05$; ‡$P < 0.005$ versus normal subjects.
Creat = creatinine.

TABLE 2
Angiotensin II infusion in normal and diabetic subjects (mean ± SEM)

		Angiotensin II infusion	
	Preinfusion	Step 1	Step 2
Infused angiotensin II dose (ng/kg/min)			
Normal subjects		3.5 ± 0.5	11.7 ± 1.1
Diabetic patients		3.2 ± 0.3	8.6 ± 1.1
Blood pressure (mm Hg)			
Normal subjects	117/71 ± 3/2	131/87 ± 4/2	150/96 ± 5/2
Diabetic patients	124/72 ± 3/2	139/83 ± 5/2	157/94 ± 5/3
Heart rate (beats/min)			
Normal subjects	70 ± 3	68 ± 3	65 ± 3
Diabetic patients	69 ± 2	66 ± 3	65 ± 3
Plasma renin activity (ng/ml/h)			
Normal subjects	1.76 ± 0.38	—	—
Diabetic patients	1.44 ± 0.43	—	—
Plasma cortisol (μg/dl)			
Normal subjects	12.1 ± 2.0	11.3 ± 1.6	12.2 ± 1.5
Diabetic patients	10.3 ± 1.6	11.3 ± 1.8	9.8 ± 1.2
Plasma 18-hydroxycorticosterone (ng/dl)			
Normal subjects	6.8 ± 1.1	11.3 ± 1.6*	12.6 ± 1.5‡
Diabetic patients	6.3 ± 0.9	11.9 ± 1.5†	13.1 ± 1.6‡
Plasma aldosterone (ng/dl)			
Normal subjects	5.1 ± 0.8	—	16.0 ± 2.5‡
Diabetic patients	2.6 ± 0.6	—	12.1 ± 1.9‡

*$P < 0.05$; †$P < 0.01$; ‡$P < 0.005$ versus corresponding preinfusion value.

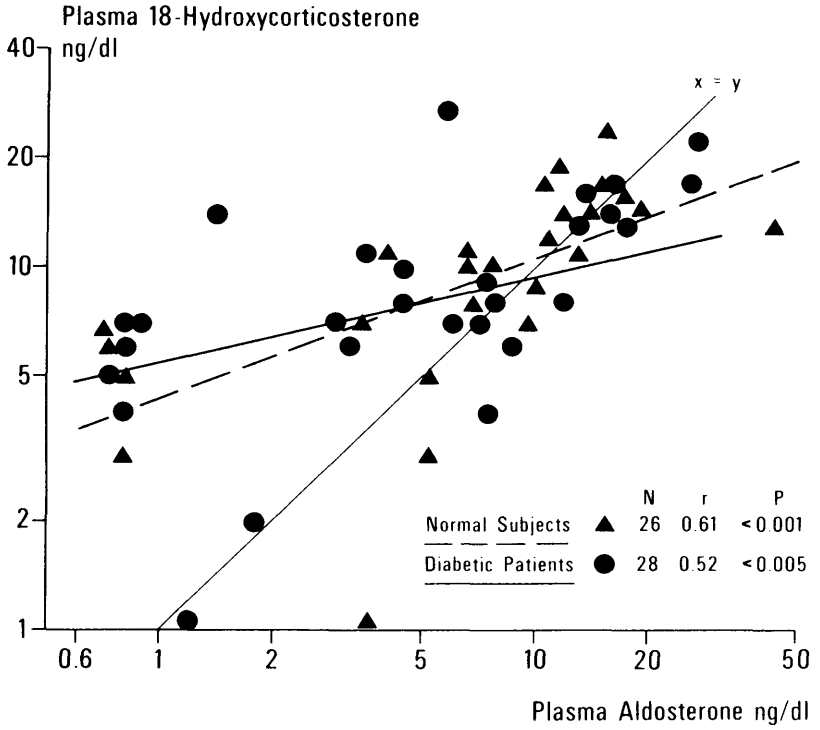

FIGURE 1. Relationship between plasma 18-hydroxycorticosterone and aldosterone concentrations before and after angiotensin II infusion in normal or diabetic subjects. The thin line represents the identity line; the dotted line, the regression line for normal subjects; and the straight line, the regression line for diabetic patients.

in normal and diabetic subjects; (2) a similar relationship between plasma 18-OH-B and A levels under basal conditions and after AII-mediated stimulation in the two groups; and (3) markedly increased levels of 18-OH-B and A after corticotropin injection in our diabetics.

Under basal conditions, plasma A levels were about 50% lower in the diabetic than in the normal subjects. This tendency was not due to differences in age, plasma renin activity, plasma potassium, or potassium intake and was unrelated to the presence or absence of diabetic complications. The diabetic patients had a tendency for low plasma epinephrine values; there is no evidence to suggest that epinephrine is important in the regulation of A secretion.[19] Exchangeable sodium is increased in the diabetic state;[11] sodium intake as judged by urinary sodium excretion also tended to be slightly higher in the present group of diabetics than in the normal control group (182 versus 141 meq/24 h). Within a range of about 50–250 meq/day, variations in sodium intake appeared to exert little influence on plasma renin activity, but correlated inversely with plasma aldosterone concentrations.[8] Excess sodium may have contributed to low levels of both aldosterone and epinephrine[20] in some of our diabetic patients.

18-OH-B is probably the immediate precursor of A.[21] Both 18-OH-B and A are synthesized in the adrenal zonal glomerulosa[21] and the secretion rates of the former steroid are about twice those of the latter.[22] Like A, plasma concentrations of 18-OH-B increase in response to upright posture, sodium deprivation, or angiotensin II infusion in normal man[23–25] and are abnormally increased in primary hyperaldosteronism.[25,26] In this study, the ratio of basal plasma 18-OH-B to A concentrations did not differ significantly between the normal and diabetic subjects, despite a tendency for a higher mean value in the latter group (2.5 versus 2.9–3.7). Previously reported ratios of plasma 18-OH-B to A levels in normal subjects lie between 1 and 2.[24,25,27] Higher ratios, ranging from 2.3 to 3.9 were noted in patients with primary hyperaldosteronism,[24,25] while the highest ratio so far (about 6) was described in diabetic patients with hyporeninemic hypoaldosteronism.[27] Based on similar findings in patients with corticosterone methyl oxidase type 2 deficiency,[28] such abnormal ratios have been taken as evidence for a disturbance of the enzymatic conversion of 18-OH-B to A. Our diabetic patients showed an intact responsiveness of A release to the acute stimuli of AII infusion or corticotropin injection; their normal plasma renin activity also contributed to exclude the presence of hyporeninemic hypoaldosteronism. Therefore, it would appear that in the absence of the biochemical signs of renin-aldosterone deficiency the function of the enzymatic pathways regulating the conversion of 18-OH-B to A is largely unaltered in patients with diabetes mellitus.

ACKNOWLEDGMENT

We thank Dr. Belkien, Division of Internal Medicine, Klinik Steglitz, Free University, Berlin, for the generous gift of 18-OH-B antiserum.

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