Aldosterone Suppression with Dopamine Infusion in Low-Renin Hypertension

O. BRYAN HOLLAND, CAROL THOMAS, HELLE BROWN, DEBORAH SCHINDEWOLF, YVONNE HILLIER, and CELSO GOMEZ-SANCHEZ, *Departments of Internal Medicine, University of Texas Medical Branch, Galveston, Texas 77550; University of Texas Health Science Center, Dallas, Texas 75235; University of South Florida College of Medicine and The James A. Haley Veterans Administration Hospital, Tampa, Florida 33612*

ABSTRACT A dopaminergic mechanism has been proposed to suppress aldosterone secretion. To assess the possibility that a defect in the dopaminergic mechanism might enhance aldosterone secretion in hypertensive patients, we determined basal and adrenocorticotropic hormone (ACTH)-stimulated plasma aldosterone (PA), cortisol, renin activity, and potassium concentrations before and during dopamine receptor stimulation with dopamine infusion and bromocriptine administration and dopamine receptor blockade with metoclopramide. The patient study groups included: (*a*) seven patients with low-renin hypertension and abnormal aldosterone suppression with sodium loading and presumed bilateral zona glomerulosa hyperplasia (ZGHP); (*b*) two patients with aldosterone-producing adenoma; (*c*) five patients with low-renin hypertension but normal aldosterone suppression with sodium loading; and (*d*) six patients with normal-renin hypertension.

Dopamine infusion in patients with ZGHP caused PA to fall ($P < 0.01$) into the normal range, but did not block the enhanced ($P < 0.05$) aldosterone response to ACTH that is characteristic of these patients. Dopamine infusion in patients with low-renin hypertension but normal aldosterone suppression also suppressed PA ($P < 0.01$), whereas it had no effect upon PA in patients with normal-renin hypertension or aldosterone-producing adenoma and did not blunt the PA response to ACTH in either group. Bromocriptine administration had no effect upon basal or ACTH-stimulated PA. Dopamine infusion in patients with ZGHP also enhanced ($P < 0.05$) diuresis and natriuresis in comparison with normal-renin patients. Metoclopramide administration increased ($P < 0.01$) PA in all patients. Thus, a dopaminergic mechanism appears to be important in the regulation of aldosterone secretion in patients with ZGHP and in other low-renin hypertensives with normal aldosterone suppression with sodium loading. In contrast, this latter group does not exhibit an enhanced aldosterone response to ACTH. Both of these groups differ from normal-renin hypertensives, who have no PA suppression with dopamine infusion.

INTRODUCTION

A dopaminergic influence on aldosterone secretion has been suggested by the observation that administration of metoclopramide, a dopamine receptor antagonist, elicits a rapid increase in plasma aldosterone concentration (PA)[1] that cannot be explained by simultaneous increases of any of the known stimuli of aldosterone secretion (1–5). Furthermore, dopamine can diminish the aldosterone response to angiotensin II in bovine adrenal cells (6). Patients with primary aldosteronism can be divided into those with aldosterone-producing adenoma and those with bilateral zona glomerulosa hyperplasia (ZGHP). Patients with ZGHP, unlike patients with aldosterone-producing adenoma, usually retain the regulatory mechanisms that decrease aldo-

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[1] *Abbreviations used in this paper:* ACTH, adrenocorticotropic hormone; D5W, 5% dextrose in water; PA, plasma aldosterone concentration; PRA, plasma renin activity; ZGHP, zona glomerulosa hyperplasia.

sterone secretion with sodium loading and increase aldosterone secretion with sodium depletion, though these mechanisms are less sensitive to changes in sodium status (7). In addition, these patients have an enhanced aldosterone response to angiotensin II (8, 9) and to ACTH (10). Recently, dopamine infusion has been shown to decrease aldosterone production (11) in some patients with aldosterone-producing adenoma, whereas plasma aldosterone concentration does not fall during dopamine infusion in normal subjects (2, 4). Tonic dopaminergic inhibition of aldosterone secretion has thus been suggested (2, 4). The influence of dopaminergic mechanisms upon aldosterone secretion in patients with ZGHP would be of great interest, as a defect in the dopaminergic mechanism would be expected to enhance aldosterone secretion. Additional interest in the evaluation of this dopaminergic mechanism has been provided by a recent report suggesting that dopamine decreases the sensitivity of aldosterone secretion in response to angiotensin II (12). The following study was performed in patients with ZGHP to evaluate the effect of dopamine receptor stimulation with bromocriptine and dopamine and of dopamine receptor antagonism with metoclopramide. Other patients with low-renin hypertension and normal aldosterone suppression with sodium loading, normal-renin hypertension, and aldosterone-producing adenoma were similarly studied for comparison.

METHODS

Secondary forms of hypertension other than primary aldosteronism were ruled out by history, physical examination, blood chemistry studies using an automated multiple analysis system (SMA-12 or SMA-24), urinalysis, urinary metanephrine, and rapid sequence intravenous pyelogram or renal scan. Renin classification was initially performed with plasma renin activity (PRA) response to 2 h of ambulation (13) or with the intravenous furosemide test (14). Those patients who appeared to have low-renin hypertension after this testing were evaluated further by determining supine and ambulatory PRA after receiving a 10-meq sodium diet for 6 d[2] or by determining ambulatory PRA after diuretic administration (13) to confirm a low-renin classification. Patients with low-renin hypertension were evaluated for primary aldosteronism with the intravenous saline infusion test (15)[2] and with a sodium loading protocol utilizing a 200-meq sodium diet for 6 d with administration of fludrocortisone acetate (Florinef, 0.5 mg/twice daily) on the last 3 d.[2] Additional studies including the PA response to upright posture, adrenal scan with NP-59, bilateral adrenal vein sampling, and adrenal computer tomographic scanning were done to distinguish patients with ZGHP from those with aldosterone-producing adenoma. The diagnosis of aldosterone-producing adenoma was ultimately confirmed by removal of the adenoma. Aldosterone, PRA, and potassium determinations in these patients are presented in Table I.

The patients were then admitted to the General Clinical Research Center for study. A diet containing 120 meq sodium and 70 meq potassium was consumed throughout the 5-d protocol. Each night the patient retired to bed between 2200 and 2400 and remained supine in bed from 0200 until the studies were completed later in the morning. At 0600 on days 2–5, an intravenous line was started and kept open with a slow infusion of 5% dextrose in water (D5W) to allow blood sampling at 30-min intervals from 0730 to 1000 on these days. At 1000, 1030, and 1100 on days 2, 4, and 5, adrenocorticotropic hormone (ACTH) was administered at a dosage of 1, 3, and 10 ng/kg, respectively, and blood was drawn 15 min later. On day 3 metoclopramide (10 mg i.v. push over 2 min) was administered at 1000 and blood was sampled 10, 20, 30, 45, 60, and 90 min afterwards. At 1800 and 2400 on day 3 and at 0600 on day 4, 2.5 mg bromocriptine was administered by mouth. At 0800 on day 5, a dopamine infusion was begun and continued at a rate of 1 ng/kg per min from 0800 to 0830, 2 ng/kg per min from 0830 to 0900, 4 ng/kg per min from 0900 to 0930, and 2 ng/kg per min from 0930 to 1130. An intravenous infusion of D5W was begun at 0800 on this day and run at a rate of 250 ml/h until 1130. Urine samples were collected on day 5 from 0600 to 0800, at hourly intervals from 0800 to 1200, and from 1200 to 1500. Blood samples were iced and centrifuged within 30 min, and the separated plasma was frozen. PA (16), cortisol (17), PRA (18), and potassium were determined. Sodium, potassium, and creatinine were determined in the urine samples.

Preliminary studies were done to assess the best method for ACTH stimulation. Iodinated ACTH was used to evaluate problems with ACTH binding to the polyethylene syringes used for administration. When dilute solutions of ACTH were left in these syringes for long periods of time (beyond 30 min), there were problems with ACTH binding. The possibility of adding human serum albumin to block this binding was considered, but this material was not used because of its high cost and possibility of trace amounts of contaminating proteases that might inactivate the ACTH. The following procedure was thus used. A stock solution of ACTH was prepared shortly before each study by mixing one ampule of Cosyntropin (0.25 mg, ACTH) with 49 ml D5W in a polyethylene syringe and refrigerated. 5-10 min before each of the three ACTH injections, 1 ml of the stock solution was mixed with 49 ml cold D5W in a polyethylene syringe to prepare a 100 ng/ml ACTH solution, and the appropriate dose was removed, warmed, and administered by rapid bolus. PA and plasma cortisol were measured 15 and 30 min after ACTH administration in the initial eight patients studied to determine the optimal time of blood sampling. PA usually was slightly higher in the 15-min sample, whereas plasma cortisol was essentially the same in both (Table II). For this reason, sampling 15 min after ACTH administration was adopted for the remaining patients. In addition, plasma dopamine concentrations were determined (19) in a subgroup of four patients to assess the circulating levels achieved during the time of dopamine infusion.

All studies were approved by the Human Research Review Committees at the University of Texas Health Science Center at Dallas or the University of Texas Medical Branch at Galveston. Statistical evaluations of the data were performed with Student's t test.

[2] Holland, O. B., H. Brown, L. Kuhnert, C. Fairchild, M. Risk, and C. E. Gomez-Sanchez. Manuscript submitted for publication.

TABLE I

Potassium, Renin, and Aldosterone Suppression with Sodium Loading in the Study Groups

Group, No.	Plasma K^+	Saline infusion: PRA, 2 h↑	Saline infusion: PA, 2 h↑	Saline infusion: PA, 4 h→	200 meq sodium diet: Supine PA	200 meq sodium diet: Ambulate PA	200 meq sodium diet: Urinary Aldo	200 meq sodium diet: Urinary THAldo	200 meq sodium diet plus Florinef: Supine PA	200 meq sodium diet plus Florinef: Ambulate PA	200 meq sodium diet plus Florinef: Urinary Aldo	200 meq sodium diet plus Florinef: Urinary THAldo
	meq/liter	*ng/ml/h*	*ng/dl*				*μg/24 h*			*ng/dl*		*μg/24 h*
Bilateral ZGHP												
1	3.7	0.9	40.5	8.3	19.2	55.4	16.2	55.8	15.0	24.3	16.2	52.3
2	3.9	0.4	25.7	8.0	34.3	60.5	20.0	129	11.7	30.1	9.2	82.2
3	4.2	0.1	18.6	3.8	10.9	27.3	6.6	35.9	7.7	34.8	6.6	28.8
4	3.6	0.4	17.1	5.4	12.7	16.6	11.7	37.5	5.5	10.2	13.4	52.9
5	2.8	0.1	45.0	18.6	28.0	71.0	17.2	96.2	30.0	68.0	18.6	117.7
6	3.3	0.7	31.7	6.0	17.1	27.0	7.9	52.7	7.1	8.2	3.9	38.9
7	3.6	0.1	27.0	9.3	15.4	19.4	15.8	79.0	7.1	13.8	11.0	81.2
Aldosterone-producing adenoma												
1	2.6	0.2	28.0	27.9	59.5	42.3	24.0	64.3	45.0	49.2	16.6	102
2	2.8	0.1	27.5	21.5								
Low-renin, normal aldosterone suppression												
	3.8 ±0.2	0.3 ±0.1	18.9 ±3.0	2.9 ±0.6	9.1 ±0.9	20.0 ±3.1	10.5 ±2.3	44.5 ±10.0	3.2 ±0.8	11.2 ±1.9	2.5 ±0.7	18.4 ±6.1
Normal-renin												
	4.0 ±0.1	1.8 ±0.7	21.5 ±11.8	3.9 ±0.5	8.3 ±1.6	19.4 ±4.2	6.2 ±1.5	37.7 ±6.5	2.4 ±0.6	3.7 ±1.2	3.8 ±0.6	19.2 ±2.8
(Normal subjects)				(<6.0	<13	<32	<17	<60	<6	<11	<6	<32)

PA, plasma aldosterone after 2 h of ambulation and after 4 h of supine posture with infusion of 2,000 ml normal saline (500 ml/h); Aldo, aldosterone; THAldo, tetrahydroaldosterone.

RESULTS

The average age, weight, PA, cortisol, PRA, and potassium concentrations (0730–1000) of the patients during the base-line phase and on the day of bromocriptine administration are presented in Table III. The data of the two patients with aldosterone-producing adenoma have been excluded from Tables III and IV

TABLE II

Comparison of PA and Plasma Cortisol Concentrations 15 and 30 min after Bolus ACTH Administration

	Patients	Base line	ACTH administered, ng/kg: 1, 15 min	1, 30 min	3, 15 min	3, 30 min	10, 15 min	10, 30 min
	n							
PA (*ng/dl*)	8	11.0±2.4	17.3±4.4	22.1±7.4	29.6±8.6	22.3±3.8	33.1±7.9	27.1±5.0
Plasma cortisol (*μg/dl*)	8	7.9±1.2	12.7±1.8	15.1±2.4	18.0±1.9	17.1±2.2	20.2±2.0	21.0±1.6

n, number of patients studied.

TABLE III

Comparison of Bromocriptine and Dopamine Administration on Average (0730–1000) PA, Cortisol, PRA, and Potassium

	Patients	Age	Weight	PA	Cortisol	PRA	Potassium
	n	*yr*	*kg*	*ng/dl*	*μg/dl*	*ng/ml/h*	*meq/liter*
Base line							
Primary aldosteronism (hyperplasia)	7	48±3	79.2±8.1	16.4±0.5	6.3±0.4	0.3±0.1	3.5±0.1
Low-renin, normal aldosterone suppression	5	53±3	72.3±5.0	11.4±0.4*	9.8±0.7*	0.4±0.1	3.7±0.1
Normal-renin	6	47±5	78±3.9	8.3±0.4*	7.2±0.9	1.2±0.1*	3.8±0.1*
Bromocriptine							
Primary aldosteronism (hyperplasia)				17.8±0.6	6.0±0.2	0.2±0.1	3.6±0.1
Low-renin, normal aldosterone suppression				10.8±0.7	9.3±0.7	0.6±0.1	3.6±0.1
Normal-renin				14.8±0.5	8.2±0.3	1.9±0.1‡	3.9±0.1
Dopamine§							
Primary aldosteronism (hyperplasia)				8.6±0.5‡	6.5±0.2	0.3±0.1	3.6±0.1
Low-renin, normal aldosterone suppression				6.7±0.3‡	9.6±0.6	0.6±0.1	3.5±0.1
Normal-renin				9.5±0.3	7.0±0.6	1.9±0.1‡	3.9±0.1

* $P < 0.01$ compared to primary aldosteronism (unpaired t test).
‡ $P < 0.01$ compared to baseline (paired t test).
§ Average values from 0830 to 1000, mean±SE.

TABLE IV

Increase in PA and Plasma Cortisol Concentrations after ACTH Administration

	ACTH dosage, ng/kg					
	Plasma aldosterone			Plasma cortisol		
	1	3	10	1	3	10
	ng/dl			*μg/dl*		
Base line						
Primary aldosteronism (hyperplasia)	18.9±7.8	25.2±6.2	33.9±10.2	4.8±2.4	6.9±2.7	8.5±1.2
Low-renin, normal aldosterone suppression	1.5±2.8	9.2±3.8	14.5±3.8	5.6±3.8	8.3±3.6	13.0±2.1
Normal-renin	1.9±0.2	4.1±1.0	9.8±1.8	1.9±0.9	5.9±1.3	12.5±1.6
Bromocriptine						
Primary aldosteronism (hyperplasia)	11.8±4.3	14.4±6.2	28.0±9.3	4.7±1.1	4.4±1.6	6.7±1.8
Low-renin, normal aldosterone suppression	6.0±5.0	7.0±3.5	11.9±2.9	1.3±3.2	5.2±2.8	6.5±1.6
Normal-renin	1.1±1.8	4.5±1.4	9.0±2.1	0.7±0.7	2.2±0.9	5.0±1.4
Dopamine						
Primary aldosteronism (hyperplasia)	15.3±7.1	27.4±8.4	30.1±8.4	3.0±0.7	6.7±1.3	9.4±1.7
Low-renin, normal aldosterone suppression	7.3±2.2	10.0±1.0	17.3±1.6	3.4±1.3	10.2±1.2	15.8±4.1
Normal-renin	4.6±1.5	9.1±3.1	16.3±6.0	4.5±1.3	6.9±0.8	11.7±1.3

* Data represent mean±SE.

owing to the small group size. The averages of similar 0830–1000 values on day 5 during the time of dopamine infusion are also presented in Table III. Patients with ZGHP had a significant ($P < 0.01$) increase in base-line PA in comparison with patients with low-renin hypertension with normal aldosterone suppression and normal-renin patients. Patients with ZGHP had a slightly lower ($P < 0.01$) plasma cortisol concentration in comparison to the other low-renin patients. PRA was essentially the same in the two low-renin groups and was diminished ($P < 0.01$) in comparison with that in normal-renin patients. Plasma potassium was slightly lower ($P < 0.01$) in patients with ZGHP in comparison with normal-renin patients. Bromocriptine administration had no effect upon PA, cortisol, PRA, or potassium concentrations, although it was associated with a slight rise ($P < 0.01$) in PRA in normal-renin patients.

Dopamine infusion resulted in the following plasma dopamine levels (mean±SE, ng/ml) in a subgroup of four patients: 0800 (before infusion)—0.11±0.02; 0830—37.7±16.4; 0900—131.2±80.4; 0930—191.8 ±90.6; 1000—158.2±78.1; 1030—80.4±29.7; 1100—83.9±22.5; 1130—51.9±8.5. Dopamine infusion caused a marked fall ($P < 0.01$) in PA into the normal range in patients with ZGHP (Table III, Fig. 1). There was a lesser, though significant ($P < 0.01$) fall in PA during dopamine infusion in patients with low-renin hypertension with normal aldosterone suppression (Table III, Fig. 2), whereas patients with normal-renin hypertension had no change in PA with dopamine infusion (Table III, Fig. 3). For unknown reasons, the 0800 average PA was slightly lower on the day of dopamine infusion that during the base line. When this 0800 PA was utilized for statistical comparison by paired t test of the 0830–1000 PA values during dopamine infusion, there was also a significant ($P < 0.05$) suppression in the ZGHP group, but not in the group with low-renin hypertension with normal aldosterone suppression with sodium loading. However, the paired comparisons to the appropriate base-line times appear more valid since this provides for known circadian variations or minor stresses in the testing procedure that might influence PA.

The changes in PA and plasma cortisol with ACTH administered at 1000, 1030, and 1100 are presented in Table IV and Figs. 1–4 and 8. Patients with ZGHP had an enhanced ($P < 0.05$) increase in PA with ACTH administration (Fig. 4). There was no significant change in the dose response to ACTH with bromocriptine administration or dopamine infusion (Figs. 1–3, 5). One patient (No. 3, Table I) had somewhat bor-

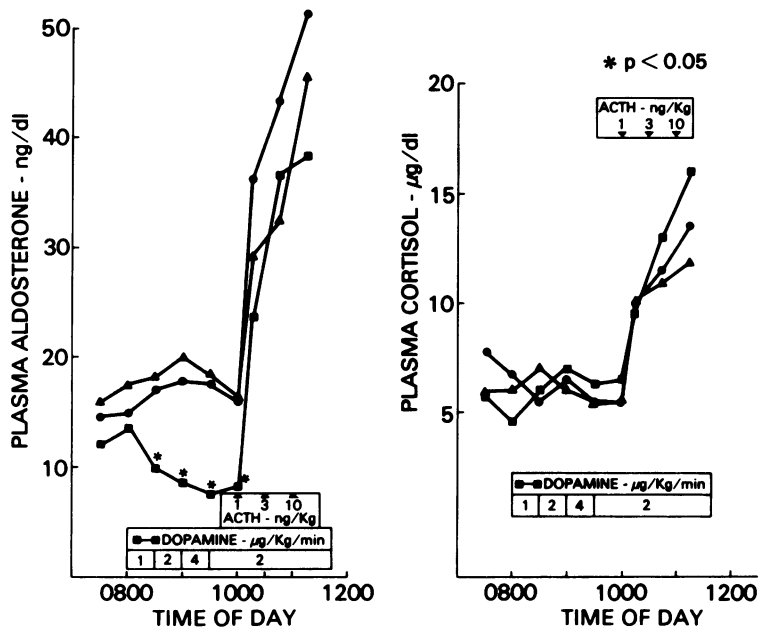

FIGURE 1 Primary aldosteronism (hyperplasia). Average PA and cortisol concentrations in patients with primary aldosteronism (hyperplasia) between 0730 and 1000 and in response to ACTH at 1000, 1030, and 1100. Base-line values (●) are compared with those obtained on another day while the patients received bromocriptine (▲) and on another day while the patients received a dopamine infusion (■) from 0800 to 1130. Significant PA suppression during dopamine infusion is indicated (*).

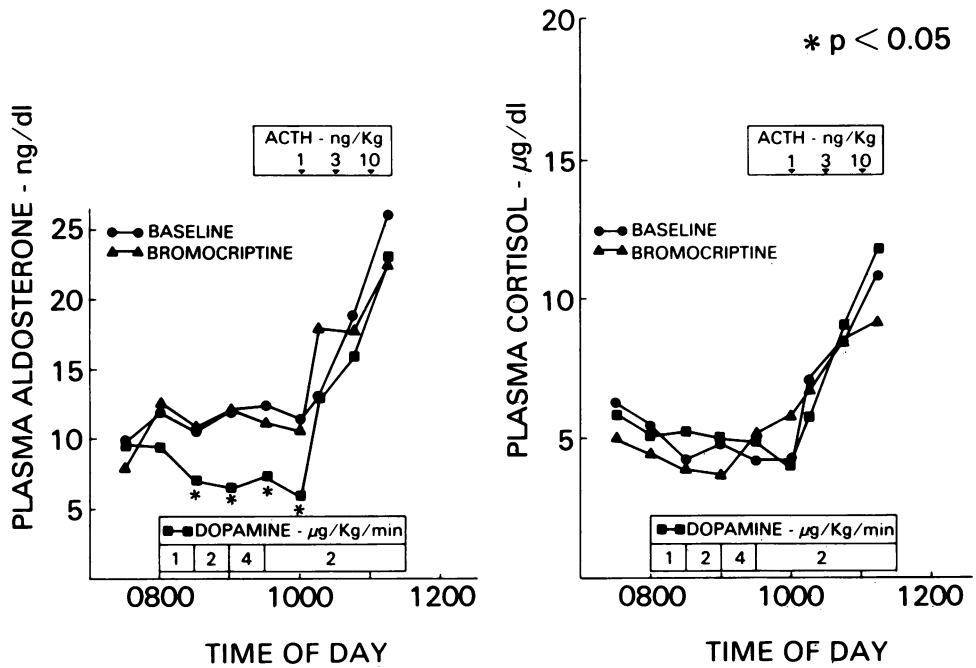

FIGURE 2 Low renin, normal aldosterone suppression. Average PA and cortisol concentrations determined as in Fig. 1 in patients with low-renin hypertension and normal aldosterone suppression with sodium loading. Significant PA suppression with dopamine infusion (■) is indicated (*). Base-line values: (●); bromocriptine administration: (▲).

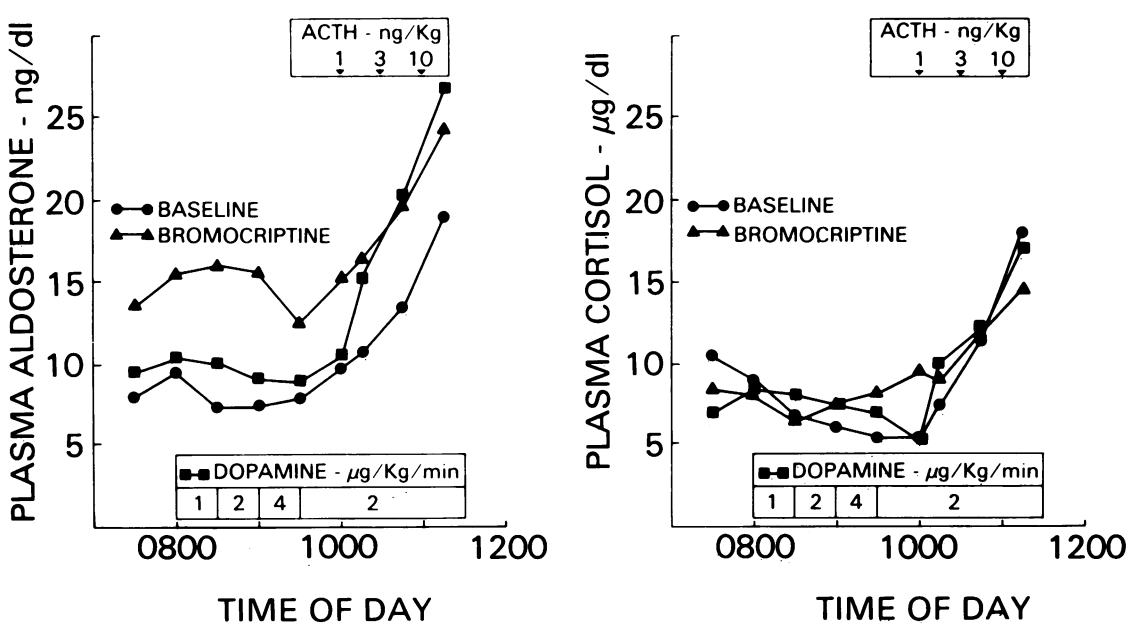

FIGURE 3 Normal renin hypertension. Average PA and cortisol concentrations determined as in Fig. 1 in patients with normal-renin hypertension. Base-line values: (●); bromocriptine administration: (▲); dopamine infusion: (■).

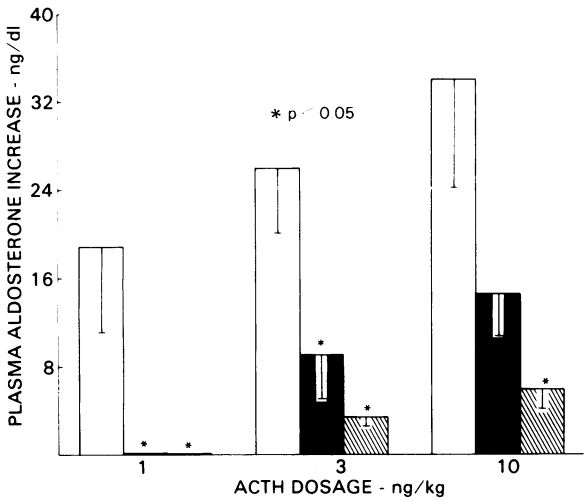

FIGURE 4 Average increase from base line of PA concentration in response to 1, 3, and 10 ng/kg ACTH (Cosyntropin) administered by intravenous bolus at 30-min intervals. Enhanced PA responses in patients with primary aldosteronism (hyperplasia [□]) over the low-renin, normal aldosterone suppression (■) and normal renin (▨) groups are indicated.

derline criteria for the diagnosis of ZGHP since there was normokalemia, normal PA suppression with saline infusion, and no elevation in PA, urinary aldosterone, and urinary tetrahydroaldosterone during the base-line phase of the Florinef protocol. Nonetheless this patient had an average 0730–1000 PA of 18.7 ng/dl in the base-line phase of this study as well as the abnormality in PA and urinary aldosterone suppression with Florinef. Dopamine infusion caused PA suppression to 3.9 ng/dl, but there was only a modest PA increase with ACTH (5.0 ng/dl with the 10 ng/kg dose). Inclusion of this somewhat questionable patient in the ZGHP group thus tended to minimize the difference in the ACTH response between this group and the other low-renin group but did not affect the conclusions from the dopamine and ACTH results.

PRA remained slightly higher ($P < 0.01$) than base line during the time of dopamine infusion, as it was on the day of bromocriptine administration. Dopamine infusion caused a diuresis in all patients, though there was a significantly greater diuresis and natriuresis in patients with ZGHP (Figs. 5, 6), whereas there was no significant increase in urinary potassium or creatinine

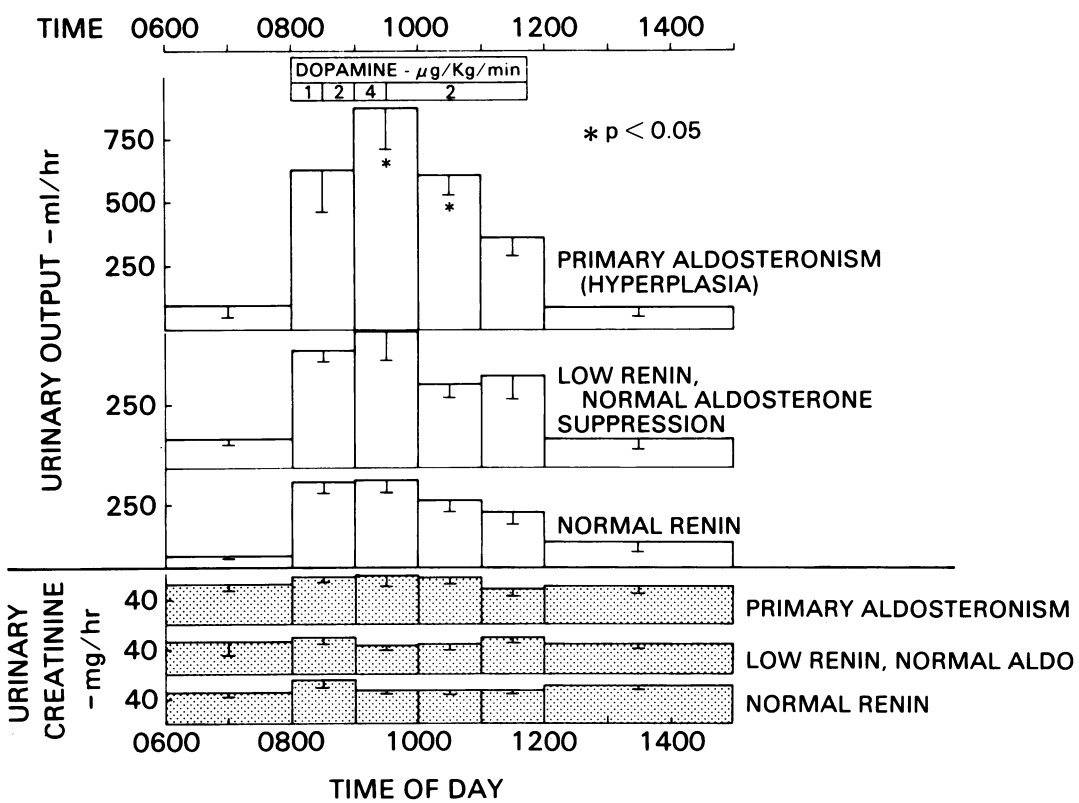

FIGURE 5 Urinary volume and creatinine before, during, and after dopamine infusion from 0800 to 1130. Increased urinary volume in patients with primary aldosteronism (hyperplasia) is indicated (*).

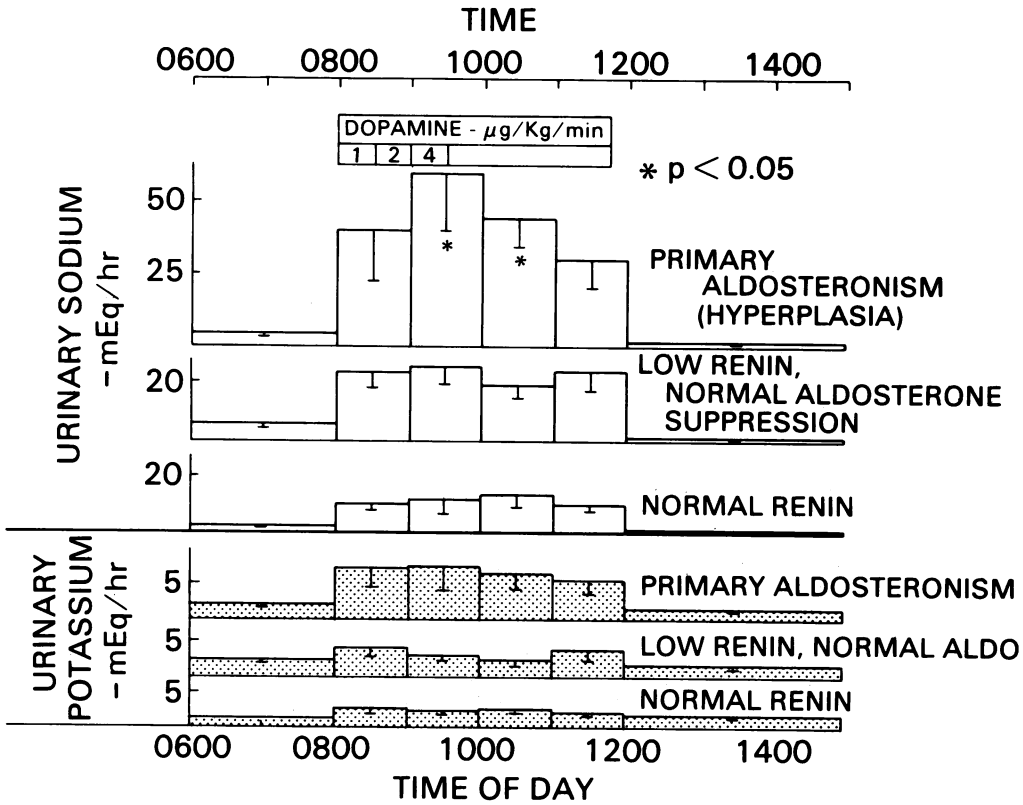

FIGURE 6 Urinary sodium and potassium output before, during, and after dopamine infusion from 0800 to 1130. Increased urinary sodium output in patients with primary aldosteronism (hyperplasia) is indicated (*).

excretion in comparison with the other two groups of patients. All patients increased ($P < 0.01$) PA in response to intravenous metoclopramide, though patients with ZGHP and low-renin patients with normal aldosterone suppression had greater ($P < 0.05$) increases than did normal-renin patients (Fig. 7). These PA changes did not appear to result from PRA or ACTH stimulation (Table V).

Two patients with aldosterone-producing adenoma were similarly studied (Fig. 8), though the studies on the day of bromocriptine administration were omitted in the second patient due to an elevation in the diastolic blood pressure to near 120 mmHg during the time of the studies. Neither dopamine infusion nor bromocriptine administration suppressed PA in either patient. However, the second patient was the only one of any of the patients studied to develop nausea secondary to the dopamine infusion. This patient developed nausea at ~0920, which diminished with decreasing the dopamine infusion rate at 0930 from 4 to 2 ng/kg per min. The nausea was associated with a rise in plasma cortisol concentration and a failure to respond to ACTH administration, thereby suggesting prominent endogenous ACTH release. Since the dose-response to ACTH administration does not appear to be blocked by dopamine infusion, the effect of dopamine infusion on PA in this patient is difficult to interpret. Both of these patients had a brisk increase in PA in response to metoclopramide administration, from 26.2 to 45.9 ng/dl in the first patient and from 28.6 to 167.1 ng/dl in the second patient. Both patients also had prominent diuresis and natriuresis during dopamine infusion, similar to patients with ZGHP (Figs. 5 and 6). The first patient increased urine volume to 940 ml/h and urinary sodium to 88 meq/h, whereas the second patient increased urinary volume to 572 ml/h and urinary sodium to 64.6 meq/h. Thus, even though these two patients had no PA suppression, they had prominent diuresis and natriuresis with dopamine infusion.

DISCUSSION

The influence of a dopaminergic mechanism in the regulation of aldosterone secretion in patients with ZGHP is unclear at present. The suppression of PA

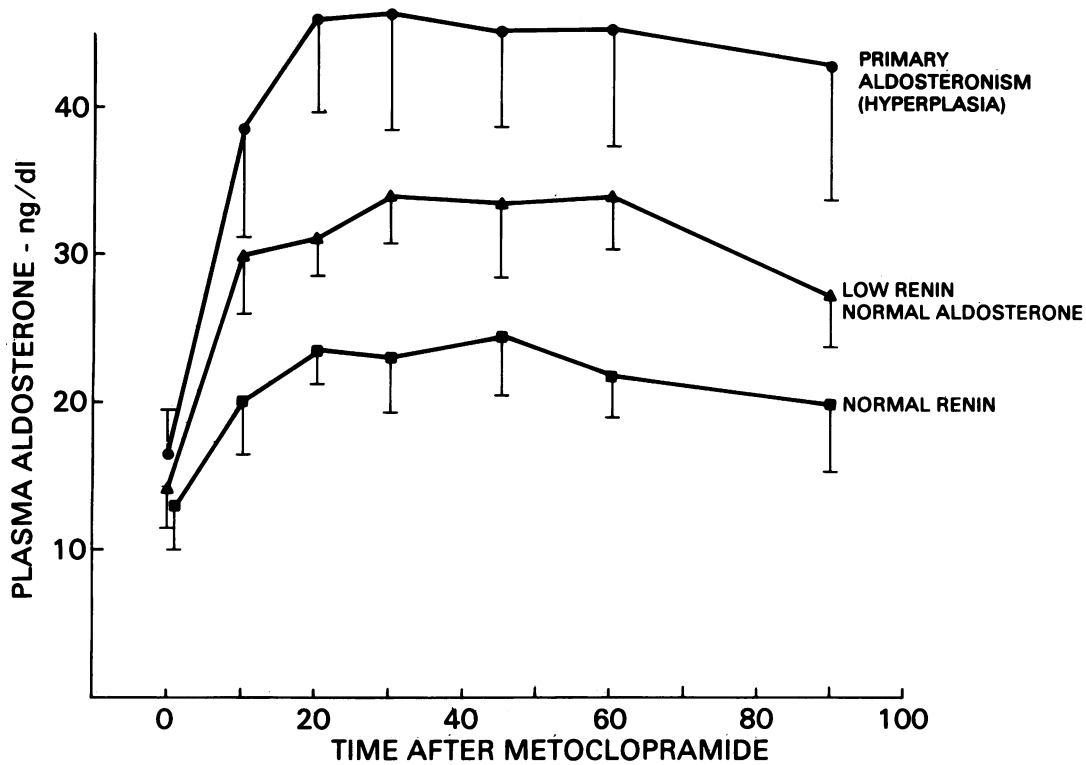

FIGURE 7 Changes in PA in response to metoclopramide (10 mg i.v.).

with dopamine infusion is compatible with either a primary or secondary phenomenon. If a primary adrenal mechanism is responsible for decreasing aldosterone secretion either directly or indirectly by inhibiting the effects of known stimuli of aldosterone secretion, then a primary loss of this mechanism would enhance aldosterone secretion. Dopamine infusion would thus restore the defective dopaminergic mechanism and would cause PA to fall. However, the apparent defective adrenal dopaminergic mechanism

TABLE V
Changes in PRA and Plasma Cortisol with Metoclopramide Administration

	Time after metoclopramide (minutes)						
	0	10	20	30	45	60	90
Primary aldosteronism (hyperplasia)							
PRA (*ng/ml/h*)	0.3±0.1	0.3±0.1	0.4±0.1	0.4±0.1	0.4±0.1	0.4±0.1	0.4±0.1
Cortisol (*μg/dl*)	4.7±1.1	5.5±1.3	4.9±0.1	6.2±0.9	7.1±1.4	5.5±1.3	4.7±1.2
Low-renin, normal aldosterone suppression							
PRA (*ng/ml/h*)	0.5±0.2	0.4±0.2	0.5±0.2	0.5±0.1	0.4±0.1	0.5±0.2	0.6±0.2
Cortisol (*μg/dl*)	7.7±2.6	8.1±2.1	10.6±1.9	12.2±1.7	11.1±2.3	13.0±1.7	12.8±1.7
Normal-renin							
PRA (*ng/ml/h*)	1.5±0.2	1.6±0.2	1.5±0.1	1.6±0.2	1.9±0.4	1.1±0.2	1.4±0.2
Cortisol (*μg/dl*)	5.7±2.1	5.0±1.1	8.6±1.3	10.7±2.0	10.6±2.6	10.5±2.9	6.2±1.2

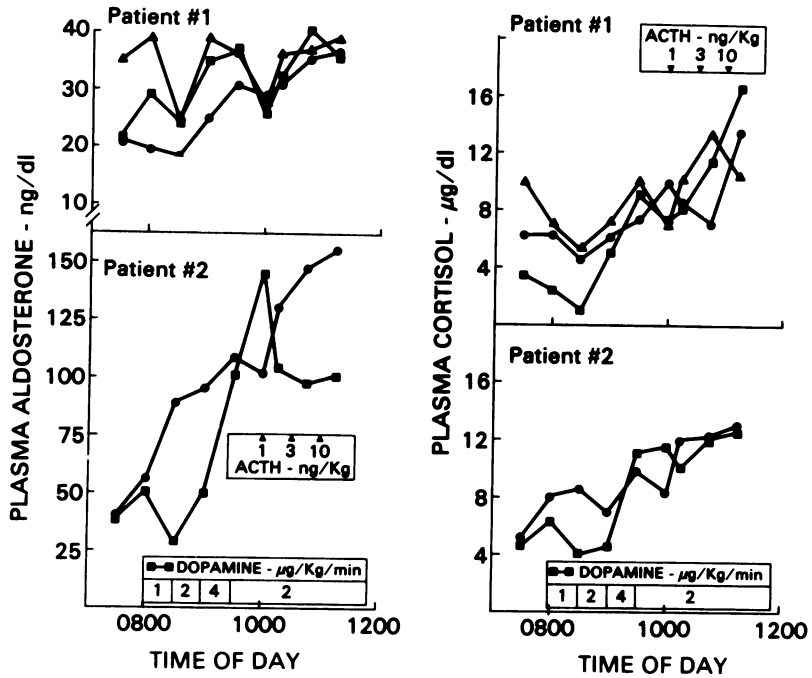

FIGURE 8 Aldosterone-producing adenoma. PA and cortisol concentrations determined as in Fig. 1 in patients with aldosterone-producing adenoma. Patient 2 developed nausea at 0920 on the day of dopamine infusion (■), which decreased after 0930 but persisted until the end of the infusion. Base-line values: (●), bromocriptine administration: (▲).

might result as a secondary phenomenon. Urinary dopamine excretion increases with sodium loading and decreases with sodium depletion (20, 21). If the adrenal dopaminergic mechanism responds similarly to changes in sodium balance, then the influence of the mechanism on aldosterone secretion would tend to decrease with sodium depletion. Aldosterone secretion is enhanced in patients with ZGHP in response to angiotensin II (8, 9) and ACTH (10) similar to that of normal individuals consuming a low-sodium diet (10). It appears that the aldosterone secretory response may be fixed in a "low-sodium" state for unknown reasons. The diminished dopaminergic influence on aldosterone secretion may be secondary to a primary adrenal alteration that fixes the zona glomerulosa in this low-sodium state. Dopamine infusion might thus be expected to diminish aldosterone secretion in these patients. An alternative possibility for a secondary phenomenon is that a presently undefined stimulus for aldosterone secretion is regulated by a dopaminergic mechanism. An attractive candidate is the recently described aldosterone-stimulating glycoprotein, which has been reported to be present in increased amounts in the urine of patients with ZGHP (8, 22, 23). If release of this factor were blocked by dopamine infusion, aldosterone secretion would be expected to fall in patients with ZGHP. However, these possibilities remain difficult to evaluate until more information is available.

The failure of PA to fall with dopamine infusion in normal-renin hypertensives and the normal stimulation with ACTH during dopamine infusion is of interest. It would appear that known stimuli of aldosterone secretion, such as angiotensin II or ACTH, appear to be much more powerful in stimulating aldosterone secretion than is dopamine in suppressing it. However, an alternative explanation is that insufficient dopamine is delivered by acute infusion to reverse the chronic zona glomerulosa changes that sensitize the aldosterone response to known stimuli such as ACTH. Aldosterone regulation would thus appear to differ in normal subjects and normal-renin hypertensives from low-renin hypertensives with or without ZGHP. During the morning when these studies were being done, ACTH would be expected to be falling slowly, and the slight decline in average plasma cortisol from 0730 to 1000 (Figs. 1-3) supports this. Low-renin patients would be expected to have low circulating levels of angiotensin II, and if this were not playing a prominent role in the regulation of aldosterone secretion in these patients, then dopamine infusion might be expected to produce aldosterone suppression more easily than

in normal-renin hypertensives or in normal subjects, who would have more substantial circulating levels of angiotensin II. These data imply that angiotensin II is not regulating aldosterone secretion in a major way in patients with low-renin hypertension. Aldosterone regulation in these patients would appear to be influenced, in a major way, either primarily or secondarily by a dopaminergic mechanism.

A further finding of interest was the lack of influence of bromocriptine administration on PA in any of the groups studied. Some investigators have noted a diminished aldosterone response to angiotensin II and diuretic administration in normal subjects or hypertensive patients administered bromocriptine chronically (24, 25), whereas these responses were not blocked with 1 d of bromocriptine therapy (3). A consistent finding has been a lack of effect of bromocriptine on basal PA (3, 24, 25). Though bromocriptine is a known dopaminergic agonist, its inability to influence aldosterone secretion would imply that it stimulates a different type of dopamine receptor than the adrenal dopamine receptor stimulated by dopamine infusion and blocked by metoclopramide. Considerable heterogeneity in dopamine receptors has been recognized (26–28). Further characterization of the adrenal dopamine receptor, which influences aldosterone secretion, might be quite helpful in developing more specific therapeutic agents for the treatment of ZGHP.

The prompt rise in PA with metoclopramide administration in patients with ZGHP as well as in other low-renin patients implies that there is not a complete loss of the dopaminergic mechanism suppressing aldosterone secretion. Other investigators have also noted an increase in PA after metoclopramide administration to patients with primary aldosteronism (5). The enhanced PA rise in patients with ZGHP is difficult to interpret. Since zona glomerulosa mass would be expected to be considerably increased in these patients in comparison to patients with normal-renin hypertension, there might be a moderate loss of the dopaminergic mechanism in the zona glomerulosa, but the increased mass of these cells might still provide a net enhanced aldosterone secretion in response to metoclopramide. This would appear to be the most likely explanation for the findings that we observed, though further studies are required to clarify these questions.

The marked increase in urinary volume and sodium excretion with dopamine infusion in patients with primary aldosteronism is of interest. This enhanced diuresis and natriuresis may reflect the response with volume-expanded hypertension to dopamine infusion. However, another interesting possibility, is that both adrenal and renal dopaminergic mechanisms are defective. A renal dopamine receptor capable of enhancing natriuresis has been identified (29, 30). If both adrenal and renal dopaminergic mechanisms were defective, sodium retention would be favored even more, and marked amplification in the level of hypertension would be expected. Bilateral adrenalectomy in patients with ZGHP has usually not reversed the hypertension (31, 32). This finding is somewhat difficult to interpret since it is quite likely that bilateral adrenalectomy has been reserved for only those patients with more severe hypertension. These patients might then have initiated secondary mechanisms that would continue the hypertension and be analogous to the experimental counterpart of metacorticoid hypertension (33). There is also some evidence that a dopaminergic mechanism unrelated to aldosterone secretion may be etiologic in the hypertension of the spontaneous hypertensive rat, since both bromocriptine and L-dopa administration reverse the hypertension in this model, whereas they cause no significant fall in blood pressure in normal controls (34, 35). Further studies would be helpful in clarifying the relationship between adrenal, renal, and systemic dopaminergic mechanisms, all of which might influence blood pressure regulation.

Suppression of PA by dopamine infusion in low-renin patients with normal aldosterone suppression with sodium loading is of interest since it suggests a certain pathophysiological kinship of the smaller group of ZGHP with the larger low-renin group. However, these patients did not have a hypersensitive aldosterone response to ACTH, as did patients with ZGHP. These data confirm our earlier failure to find enhanced aldosterone response to ACTH in the majority of patients with low-renin "essential" hypertension in comparison with normal subjects (10). However, in this earlier report (10) we noted that a subgroup of these low-renin patients had aldosterone responsiveness to ACTH indistinguishable to that of patients with primary aldosteronism due to either ZGHP or aldosterone-producing adenoma, suggesting that more complete evaluation of aldosterone regulation in low-renin patients might identify patients with subtle ZGHP more correctly. Nonetheless, as discussed earlier, since the zona glomerulosa mass in these low-renin patients with normal aldosterone suppression might be smaller than in patients with ZGHP, the zona glomerulosa sensitivity to ACTH might be identical to that in ZGHP, but there still might not be an enhanced rise in PA. We noted that two of the five low-renin patients with normal aldosterone suppression had 0730–1000 PA levels part of the time that overlapped with the lower range of PA values in some of the patients with ZGHP. Thus, it is possible that some of these patients have even milder forms of ZGHP. Since there is evidence that patients with ZGHP have a hypertensinogenic

mechanism in addition to the abnormality in aldosterone regulation (31, 32), then a different balance of these two mechanisms might result in a patient being classified as ZGHP or as low-renin hypertension with normal aldosterone suppression. We have utilized abnormal aldosterone suppression in response to sodium loading as a means of classifying low-renin patients as having ZGHP. However, the accuracy of a means of separating these patients from other types of low-renin hypertensives will remain unknown until more is understood about the etiology of ZGHP. However, it would appear that all of these low-renin patients are not variants of essential hypertension, since there was no suppression of PA with dopamine infusion in patients with normal-renin hypertension. Further studies are required to clarify the importance of dopaminergic mechanisms in regulating aldosterone secretion and in blood pressure control.

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REFERENCES

1. Norbiato, G., M. Bevilacqua, U. Raggi, P. Micossi, and C. Morini. 1977. Metoclopramide increases plasma aldosterone concentration in man. *J. Clin. Endocrinol. Metab.* 45:1313–1316.
2. Carey, R. M., M. O. Thorner, and E. M. Ortt. 1980. Dopaminergic inhibition of metoclopramide-induced aldosterone secretion in man. Dissociation of responses to dopamine and bromocriptine. *J. Clin. Invest.* 66:10–18.
3. Carey, R. M., M. O. Thorner, and E. M. Ortt. Effects of metoclopramide and bromocriptine on the renin-angiotensin-aldosterone system in man. Dopaminergic control of aldosterone. *J. Clin. Invest.* 63:727–735.
4. Noth, R. H., R. W. McCallum, C. Contino, and J. Havelick. 1980. Tonic dopaminergic suppression of plasma aldosterone. *J. Clin. Endocrinol. Metab.* 51:64–69.
5. Mantero, F., G. Opocher, M. Boscaro, E. Valpione, D. Armanini, and F. Fallo. 1981. Effects of metoclopramide on plasma aldosterone in normal subjects, primary aldosteronism, and hypopituitarism. *Horm. Metab. Res.* 464–467.
6. McKenna, T. J., D. P. Island, W. E. Nicholson, and G. W. Liddle. 1979. Dopamine inhibits angiotensin-stimulated aldosterone biosynthesis in bovine adrenal cells. *J. Clin. Invest.* 64:287–291.
7. Rodriguez, J. A., J. M. Lopez, and E. G. Biglieri. 1981. DOCA test for aldosteronism: its usefulness and implications. *Hypertension.* 3(Suppl. I):II-102-II-106.
8. Brown, R. D., M. Wisgerhof, P. C. Carpenter, G. Brown, N. S. Jiang, P. Kao, and R. Hegstad. 1979. Adrenal sensitivity to angiotensin II and undiscovered aldosterone-stimulating factors in hypertension. *J. Steroid. Biochem.* 11:1043–1050.
9. Fraser, R., C. Beretta-Piccoli, J. J. Brown, A. M. M. Cumming, A. F. Lever, P. A. Mason, J. J. Morton, and J. I. S. Robertson. 1981. Response of aldosterone and 18-hydroxycorticosterone to angiotensin II in normal subjects and patients with essential hypertension, Conn's syndrome, and nontumorous hyperaldosteronism. *Hypertension.* 3:(Suppl. I):I-87-I-92.
10. Kem, D. C., M. H. Weinberger, J. R. Higgins, N. J. Kramer, C. Gomez-Sanchez, and O. B. Holland. 1978. Plasma aldosterone response to ACTH in primary aldosteronism and in patients with low-renin hypertension. *J. Clin. Endocrinol. Metab.* 46:552–560.
11. Hollifield, J. W., S. D. Winn, M. G. Fraser, and D. Latta. 1979. Dopamine suppression of aldosterone production in man. *Clin. Res.* 27:739*a*. (Abstr.)
12. Gordon, M. B., T. J. Moore, R. G. Dluhy, and G. H. Williams. 1983. Dopaminergic modulation of aldosterone responsiveness to angiotensin II with changes in sodium intake. *J. Clin. Endocrinol. Metab.* 56:340–345.
13. Holland, O. B., C. E. Gomez-Sanchez, C. Fairchild, and N. M. Kaplan. 1979. Role of renin classification for diuretic treatment of black hypertensive patients. *Arch. Intern. Med.* 139:1365–1370.
14. Kaplan, N. M., D. C. Kem, O. B. Holland, N. J. Kramer, J. Higgins, and C. Gomez-Sanchez. 1976. The intravenous furosemide test: a simple way to evaluate renin responsiveness. *Ann. Intern. Med.* 84:639–645.
15. Kem, D. C., M. H. Weinberger, D. M. Mayes, and C. A. Nugent. 1971. Saline suppression of plasma aldosterone in hypertension. *Arch. Intern. Med.* 128:380–395.
16. Gomez-Sanchez, C., D. C. Kem, and N. M. Kaplan. 1973. A radioimmunoassay for plasma aldosterone by immunologic purification. *J. Clin. Endocrinol. Metab.* 36:795–798.
17. Gomez-Sanchez, C., L. Milewich, and O. B. Holland. 1977. Radioiodinated derivatives for steroid radioimmunoassay. Application to the radioimmunoassay of cortisol. *J. Lab. Clin. Med.* 89:902–909.
18. Haber, E. T., T. Koerner, L. B. Page, B. Kliman, and A. Purnode. 1969. Application of a radioimmunoassay for angiotensin I to the physiologic measurements of plasma renin activity in normal human subjects. *J. Clin. Endocrinol. Metab.* 29:1349–1355.
19. Durrett, L. R., and M. G. Ziegler. 1980. A sensitive radioenzymatic assay for catechol drugs. *J. Neurosci. Res.* 5:587–598.
20. Carey, R. M., G. R. Van Loon, A. D. Baines, and E. M. Orth. 1981. Decreased plasma and urinary dopamine during dietary sodium depletion in man. *J. Clin. Endocrinol. Metab.* 52:903–909.
21. Alexander, R. W., J. R. Gill, Jr., H. Yamabe, W. Lovenburg, and H. R. Keiser. 1974. Effects of dietary sodium and of acute saline infusion on the interrelationship be-

tween dopamine excretion and adrenergic activity in man. *J. Clin. Invest.* 54:194–200.
22. Sen, S., R. Valenzuela, R. Smeby, E. L. Bravo, and F. M. Bumpus. 1981. Localization, purification, and biological activity of a new aldosterone-stimulating factor. *Hypertension.* 3:I-81-I-86.
23. Sen, S., J. R. Shainoff, E. L. Bravo, and F. M. Bumpus. 1981. Isolation of aldosterone-stimulating factor (ASF) and its effect on rat adrenal glomerulosa cells in vitro. *Hypertension.* 3:4–10.
24. Whitfield, L., J. R. Sowers, M. L. Tuck, and M. S. Golub. 1980. Dopaminergic control of plasma catecholamine and aldosterone responses to acute stimuli in normal man. *J. Clin. Endocrinol. Metab.* 51:724–729.
25. Birkhauser, M., A. Riondel, and M. B. Vallaton. 1979. Effect of angiotensin II, ACTH, and upright posture on plasma aldosterone levels in subjects receiving bromergocryptine. *Acta Endocrinol. (Copenh.).* 91:294–302.
26. Costall, B., and R. J. Naylor. 1981. The hypotheses of different dopamine receptor mechanisms. *Life Sci.* 28:215–229.
27. Kebabian, J. W., and D. B. Calne. 1979. Multiple receptors for dopamine. *Nature (Lond.).* 277:93–96.
28. Volkman, P.H., J. D. Kohli, L. I. Goldberg, J. G. Cannon, and T. Lee. 1977. Conformational requirements for dopamine-induced vasodilation. *Proc. Natl. Acad. Sci. USA.* 74:3602–3606.
29. Goldberg, L. I. 1972. Cardiovascular and renal actions of dopamine: potential clinical applications. *Pharmacol. Rev.* 24:1–29.
30. McDonald, R. H., Jr., L. I. Goldberg, J. L. McNay, and E. P. Tuttle, Jr. 1964. Effects of dopamine in man: augmentation of sodium excretion, glomerular filtration rate, and renal plasma flow. *J. Clin. Invest.* 43:1116–1124.
31. Biglieri, E. G., M. Schambelan, P. E. Slaton, J. R. Stockigt. 1970. The intercurrent hypertension of primary aldosteronism. *Circ. Res.* 26/27(Suppl. I):I-95-I-202.
32. Baer, L., S. C. Sommers, L. R. Krakoff, M. A. Newton, and J. H. Laragh. 1970. Pseudoprimary aldosteronism. An entity distinct from true primary aldosteronism. *Circ. Res.* 26/27(Suppl. I):I-203-I-216.
33. Sturtevant, F. M. 1958. The biology of metacorticoid hypertension. *Ann. Intern. Med.* 49:1281–1293.
34. Judy, W. V., A. M. Watanabe, D. P. Henry, H. R. Besch, Jr., and B. Aprison. 1978. Effect of L-dopa on sympathetic nerve activity and blood pressure in the spontaneously hypertensive rat. *Circ. Res.* 43:24–28.
35. Sowers, J. R. 1981. Effects of bromocriptine on responses to stress in spontaneously hypertensive rats. *Hypertension.* 3:544–550.