Relation between Potassium Balance and Aldosterone Secretion in Normal Subjects and in Patients with Hypertensive or Renal Tubular Disease *

PAUL J. CANNON, RICHARD P. AMES, AND JOHN H. LARAGH †

(*From the Department of Medicine, College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York, N. Y.*)

The mechanisms that control the adrenal secretion of aldosterone are not completely understood. Recent evidence suggests that the release of renin from the kidneys with subsequent stimulation of aldosterone secretion by angiotensin may play a major role in the regulation of sodium balance (1–7). Furthermore, the secretion of renin has been linked to changes in sodium balance (8–10).

Through its action on the kidneys aldosterone not only influences sodium excretion but also plays an important role in the regulation of potassium balance. Since potassium balance may change independently of sodium balance, the possibility must be recognized that changes in potassium balance could also play an important role in the regulation of aldosterone secretion. Previous studies have shown that potassium administration can stimulate aldosterone secretion in the dog (11, 12), and balance studies in man have indicated that changes in potassium intake exert slight effects on urinary excretion of aldosterone (13–17).

For this reason and because situations exist in which hypersecretion of aldosterone occurs without clinical evidence to suggest marked angiotensinemia the present study was undertaken to define in man, under conditions in which sodium intake was rigidly controlled, the character of the aldosterone response to changes in potassium balance.

The data demonstrate that potassium salt administration stimulates aldosterone secretion in normal man. Depending upon the state of sodium balance or the disease state present, the magnitude of the stimulus to aldosterone secretion produced by potassium administration can equal or exceed that produced by an infusion of angiotensin II.

Methods

The 23 normal volunteers and the 23 patients who participated in this study were admitted to the metabolism ward where they were given a constant daily diet of known electrolyte content. The subjects received the control diet for at least 4 to 6 days before a study was started.

Patients with elevated blood pressures but no evidence of cardiac or retinal complications were classified as primary (benign essential) hypertension (6). Patients with high blood pressures and evidence of renal or retinal complications were classified as advanced hypertension (4). Criteria for retinal complications were the presence of hemorrhages or exudates. Renal complications were defined as the presence of proteinuria (2+) or a blood urea nitrogen greater than 30 mg per 100 ml. Patients with unequivocal papilledema were classified as malignant hypertension. Hypertensive patients with renal arterial stenosis were verified by aortography or at operation (7). Each of the three hypertensive patients with primary aldosteronism had oversecretion of aldosterone that was corrected by removal of an adrenal tumor. No patient with a blood urea nitrogen greater than 45 mg per 100 ml was studied.

The patient with renal tubular acidosis was a 33-year-old female with a clinical syndrome (18) characterized by inability to lower urinary pH below 6.3, hypokalemia, nephrocalcinosis, and a normal level of blood urea nitrogen. Balance data suggested impairment of renal sodium conservation. The other patient with nephropathy was an 11-year-old Negro boy with clinical features similar to patients with the syndrome of primary juxtaglomerular complex hyperplasia (19). He was not edematous, had normal levels of blood pressure and blood urea nitrogen, and exhibited severe renal

wastage of potassium, impaired ability to conserve sodium, and a marked hypokalemic alkalosis.

Potassium was administered orally four times daily as the chloride salt (20% solution) or as an aqueous mixture of potassium citrate, bicarbonate, and gluconate. A negative K^+ balance was induced by the administration of a nutritionally adequate milk product diet [1] that contained 5 mEq of sodium and 3 to 5 mEq of potassium per day. Potassium depletion was also induced by oral administration of 0.5 g chlorothiazide, 50 mg hydrochlorothiazide, or 50 mg ethacrynic acid, all given four times daily. In every situation involving altered potassium balance the plasma potassium concentration or the electrocardiograms, or both, were monitored frequently.

Metabolic ward techniques and the analytical methods for the measurement of plasma and urinary electrolytes and blood urea nitrogen have been reported previously (20, 21). Venous blood for measurement of plasma electrolytes was drawn each morning 60 to 90 minutes after an oral K^+ load. Serial determinations throughout the day in eight patients revealed that in most subjects peak blood levels occurred at this time. Aldosterone secretion rates were measured by an isotope dilution technique in which 7 or 1-2 tritium-labeled aldosterone [2] that had been checked for purity and stability was utilized. One to 2 μc of the labeled hormone dissolved in 5 to 10 ml of 10% ethanol was injected intravenously at the beginning of each study. The subsequent 24-hour urine was incubated at pH 1 for 24 hours. The aldosterone liberated by this procedure was identified by paper chromatography, eluted, and then acetylated with acetic anhydride-^{14}C to form aldosterone diacetate. After further chromato-

graphic purification on a paper and on a Celite column the ^{3}H to ^{14}C ratio of the purified sample was determined, and from this the 24-hour secretion rate of aldosterone was calculated utilizing standard isotope dilution equations. The final values were corrected for isotope displacement (22). Twenty-four-hour excretion rates of the acid labile conjugate of aldosterone were also measured by the same principle and analytic procedures. For the latter determination, however, a known amount of the labeled hormone was added to the urine after hydrolysis but before extraction. By these methods normal subjects on unrestricted diets may exhibit secretion rates ranging from 75 to 300 μg per day and excretion rates from 7 to 30 μg per 24 hours, with the variation depending to a great extent on the sodium intake.

Results

The results of 69 metabolic balance studies (of from 5 to 30 days in duration) carried out on 46 subjects are presented in Figures 1 to 7 and Tables I to III.

Potassium administration to normal subjects

Normal sodium diet. In Table I and Figure 1 data are presented from balance studies of four normal volunteers who received potassium chloride by mouth (104 and 160 mEq per day) for 4 to 6 days. Potassium supplements produced modest increases in both aldosterone secretion rates (+ 103 and + 55 μg per 24 hours) and aldosterone excretion rates (+ 33 and + 5 μg per 24 hours). The induced increases in plasma potas-

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[1] Prepared by Mead Johnson Laboratories, Evansville, Ind.

[2] U. S. Public Health Service.

TABLE I

Effect of potassium administration upon the aldosterone secretion and excretion of normal subjects

| Date	Diet Na$^+$	Diet K$^+$	Aldosterone secretory rate	Excretion rate	Weight	Volume	Urinary Na$^+$	Urinary K$^+$	Urinary Cl$^-$	Plasma K$^+$
	mEq/24 hours		*μg/24 hours*		*kg*	*ml/24 hours*	*mEq/24 hours*			*mEq/L*
Normal sodium diet + potassium chloride NJ, 34-year-old male										
3/8	86	103		34.6	66.3	1,670	65	98	82	
3/9	86	103	289		66.2	1,500	57	87	76	
3/10	86	264			66.4	1,740	116	223	249	5.4–11 a.m.; 5.1–12 noon 5.1– 1 p.m.
3/11	86	264			66.4	1,540	96	223	261	4.5
3/12	86	264			66.3	1,580	72	243	258	4.6
3/13	86	264		67.9	66.3	1,340	65	253	254	4.7– 9 a.m.; 5.3–12 noon
3/14	86	264	419		66.4	1,600	71	238	240	4.0
3/15	86	103		34.4	66.2	1,150	38	109	89	5.4
3/16	86	103	291		66.5	1,400	66	96	84	
Low sodium diet + potassium chloride GR, 31-year-old male										
5/9	17	115	336		73.2	2,030	27	76	18	
5/10	17	115		41	73.2	2,000	30	85	27	
5/11	17	115	317		73.4	1,700	14	90	85	4.2
5/12	17	275			72.7	2,240	28	239	135	
5/13	17	275			73.3	1,740	24	104	172	
5/14	17	275		73	72.9	2,380	37	342	211	
5/15	17	275	980		72.7	2,260	37	285	224	4.8
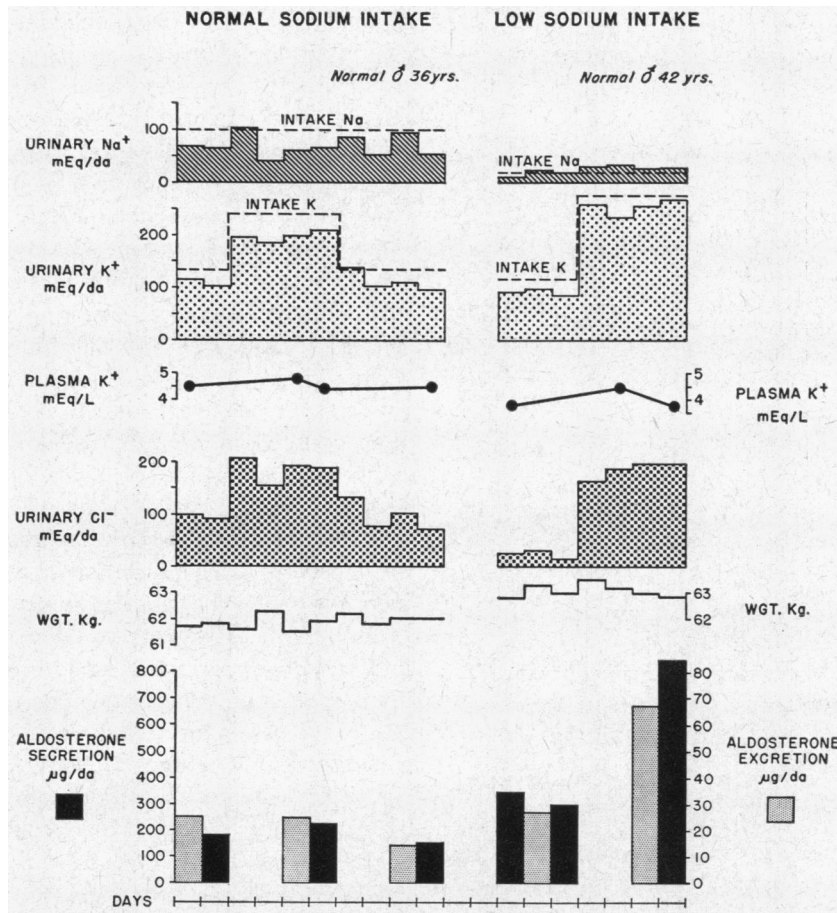
Fig. 1. Potassium administration and aldosterone secretion in normal subjects—modifying influence of sodium balance. K^+ administration had very little effect on the secretory and excretory rates of aldosterone when sodium intake was normal. However, in a sodium-deprived normal subject feeding of similar amounts of potassium caused a striking increase in aldosterone secretion.

sium concentration did not exceed + 0.3 mEq per L. A marked rise in urinary K^+ output occurred. There were no consistent changes in urinary sodium excretion or in body weight. In 15 similar balance studies in which an average of 120 mEq of potassium was added to a normal sodium diet for 4 to 6 days, the secretion rate of aldosterone rose by a mean of 107 μg per 24 hours (Figure 2). Both the secretion and excretion rates of aldosterone returned to control values a few days after potassium supplements were stopped.

Low sodium diet. In contrast, the administration of similar amounts of potassium (mean, 150 mEq of K^+ orally per 24 hours) for 4 to 6 days produced much larger increases in the aldosterone secretion and excretion rates of normal subjects

after sodium depletion. Sodium depletion was achieved by a low salt diet alone in six studies and by a low salt diet combined with administration of saliuretic diuretics (four studies). As illustrated by two representative studies presented in detail (Table I, Figure 1) potassium administration usually caused neither significant natriuresis nor loss of weight. Plasma concentrations of potassium increased, but they remained in the same range (3.5 to 5.5 mEq per L) as in the studies of subjects who received a normal sodium intake.

In ten studies of salt-depleted normal subjects the mean increment in aldosterone secretion induced by potassium feeding was 841 μg per 24 hours (Figure 2). During K^+ administration in studies of this group the mean change in plasma
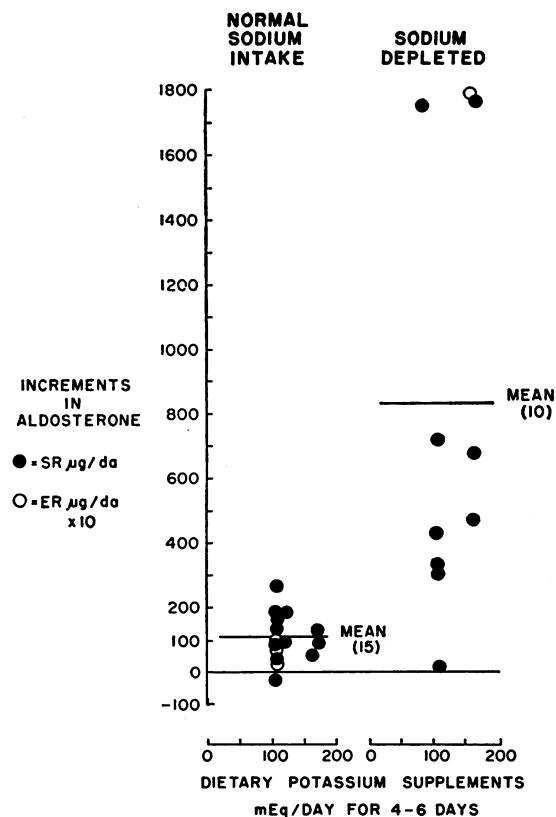
FIG. 2. INCREMENTS IN ALDOSTERONE SECRETION AND EXCRETION PRODUCED BY POTASSIUM ADMINISTRATION IN NORMAL SUBJECTS—THE MODIFYING INFLUENCE OF SODIUM DEPLETION. When the subjects were maintained on a normal sodium intake, the mean increment in aldosterone secretion was + 107 μg per day. This was associated with a mean weight gain of 1.1 kg and a mean change in plasma K^+ of − 0.1 mEq per L. However, after sodium depletion potassium increased aldosterone secretion by a mean of + 841 μg per day. This effect was associated with mean changes of + 0.5 kg in weight and + 0.7 mEq in plasma potassium. SR = secretion rate; ER = excretion rate.

potassium concentration was + 0.7 mEq per L; mean weight change was + 0.51 kg. The greatest increments in aldosterone secretion that were induced by potassium occurred in four subjects in whom the degree of sodium depletion had been increased by the administration of saliuretic diuretics 4 to 6 days before onset of the study.

Potassium depletion in normal subjects

Normal sodium diet. In two normal subjects (Figure 3, Table II) the administration of a sup-

plemented synthetic diet containing 86 to 102 mEq of sodium and 3 to 5 mEq of potassium per day was followed by significant reductions in the adrenal secretion rate of aldosterone (− 52 and − 202 μg per 24 hours). During this period potassium balance was negative (cumulative K^+ balances: − 166 and − 122 mEq K^+), and a moderate hypokalemia (plasma $[K^+]$, 3.5 and 3.7 mEq per L) ensued. Both subjects maintained a normal sodium balance.

Low sodium diet. In two other normal subjects (Figure 3, Table II) administration of an artificial diet deficient both in sodium and potassium resulted in negative sodium and potassium balances (cumulative K^+ balances: − 196 and − 124 mEq K^+) and modest falls in plasma potassium concentration (plasma $[K^+]$, 3.3 and 3.2 mEq per L). The secretion rate of aldosterone increased somewhat in the subjects (+ 162 and + 213 μg per 24 hours); however, the normal rise in aldosterone secretion usually observed after sodium restriction (23) was considerably blunted. In one of the subjects (Figure 4) the administration of oral K^+ after 6 to 7 days induced a sharp rise in aldosterone secretion (+ 310 μg per 24 hours) to the expected high levels, but only a slight rise (+ 0.8 mEq per L) in plasma $[K^+]$.

Diuretic-induced potassium depletion. In 11 studies diuretic agents known to increase potassium excretion were administered to normal subjects for periods of from 5 to 26 days. In five studies 80 mEq or more of dietary NaCl was given in the daily diet; in six studies the diet contained only 14 to 17 mEq NaCl daily. Two representative studies of one subject appear in Figure 4. Both ethacrynic acid and hydrochlorothiazide induced natriuresis, diuresis, and loss of weight; mean weight loss for the group was 2.4 kg. Both induced significant renal K^+ loss (e.g., Figure 4, cumulative K^+ balances: − 442 and − 515 mEq K^+) and hypokalemia (mean fall in 11 studies, 1.3 mEq per L; range, 0.5 to 2.3 mEq per L). However, in contrast to the effects of dietary Na^+ and K^+ depletion, aldosterone secretion rates rose to very high levels after administration of these diuretics, despite much greater potassium losses and greater degrees of hypokalemia than had been produced by dietary deprivation (Figure 4). The mean increment in daily aldosterone secretion induced by the administration of chlorothiazide, hy-
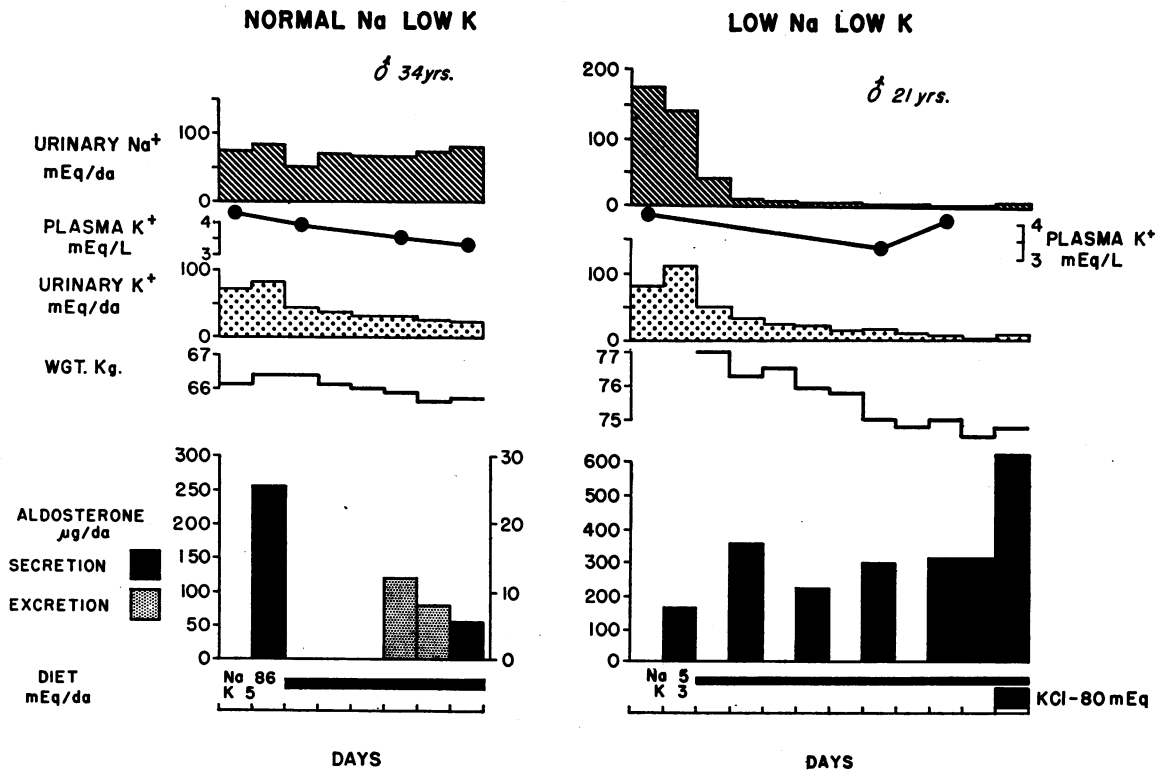
FIG. 3. DIETARY POTASSIUM DEPRIVATION IN NORMAL SUBJECTS. When subjects were maintained on a constant normal sodium diet, potassium deprivation caused aldosterone secretion to fall. In the subject on the right, simultaneous potassium and sodium deprivation blunted the usual use in aldosterone secretion of sodium deprivation. On the final day KCl repletion markedly stimulated aldosterone secretion.

drochlorothiazide, or ethacrynic acid in the 11 studies was + 777 µg per 24 hours.

In three other studies in which a negative sodium balance did not result from diuretic administration, the secretion rate of aldosterone did not change or fell concomitant with diuretic-induced negative potassium balance. Oral administration of ethacrynic acid with 20 g of supplemental NaCl for 4 to 5 days in two subjects resulted in a fall in plasma [K⁺] (− 1.9, − 1.5 mEq per L), little change in weight (+ 0.4 kg, − 0.9 kg) with no change in aldosterone secretion in one subject and a slight fall (− 87 µEq per 24 hours) in the other. In a third subject whose aldosterone secretion rate had reached very high levels after prolonged salt depletion and administration of ethacrynic acid, the oral administration of chlorothiazide (2 g daily for 8 days) did not induce further natriuresis but caused a significant kaliuresis with a fall of serum [K⁺] to 2.5 mEq per L. This was associated with a decline in aldosterone secretion

from 3,150 µg per 24 hours to 1,008 µg per 24 hours.

Potassium administration in arterial hypertension

Primary hypertension. Six patients with essential hypertension were studied similarly. Four received a normal sodium intake (82 to 107 mEq dietary sodium daily). Two were sodium depleted (11 mEq Na⁺ per day). Each patient received 87 to 107 mEq of potassium salts orally for 4 to 6 days.

The aldosterone responses observed (Table III) were qualitatively similar but smaller than those observed in normal subjects (Figure 2). When maintained on a normal sodium diet either a slight rise or a fall in aldosterone secretion or excretion occurred during potassium feeding. The mean increment in aldosterone secretion observed in the four patients was + 7 µg per 24 hours. In two other hypertensive subjects who had previously

been sodium depleted aldosterone secretion rose by a mean of 410 μg per 24 hours in response to potassium administration.

Hypertension secondary to renal arterial stenosis. Nine similar studies were performed on seven patients with hypertension secondary to renal arterial stenosis (Table III); 107 mEq of KCl was administered orally for 4 to 7 days. All these subjects received a normal (82 to 107 mEq per 24 hours) sodium intake.

Control aldosterone secretion rates in this group ranged from 112 μg per day (HOL) to 783 μg per day (CAC). The values tended to be higher in patients with higher diastolic pressures or in those who manifested hypokalemia.

The increments in aldosterone secretion produced by potassium in this group of patients ranged from +110 to +1,165 μg per 24 hours and averaged +507 μg per 24 hours. This was associated with rises in plasma K$^+$ concentration that averaged +0.8 mEq per L and with variable changes in weight (mean − 0.8 kg).

Advanced and malignant hypertension. Four patients with advanced hypertension received po-

tassium supplements while on a normal sodium intake (Table III). Control values for aldosterone secretion were slightly elevated in these patients (295 to 552 μg per 24 hours). Potassium administration caused significant increases in aldosterone output (+266 to +784 μg per 24 hours). The mean increment in aldosterone of +434 μg per 24 hours was accompanied by a mean change in plasma [K$^+$] of +1.1 mEq per L and a mean weight change of +0.2 kg. Subsequent sodium depletion in one patient (BUL) increased her aldosterone response to potassium (Table III).

The elevated aldosterone secretion rates of two patients with malignant hypertension increased more than twofold in response to potassium (+ 1,297 and + 1,500 μg per 24 hours). Both of these patients received a normal sodium intake during the study. A detailed balance of one (LU) who progressed from advanced to malignant hypertension appears in Figure 5. In this patient a negative sodium balance did not accompany the large increment in aldosterone secretion induced by potassium. A greater rise in aldosterone out-

TABLE II

Effect of dietary potassium depletion upon aldosterone secretion of normal subjects

| Date | Diet | | Aldosterone secretion | Weight | U$_{Na}$$^+$V* | U$_K$$^+$V* | Plasma K$^+$ |
	Na$^+$	K$^+$					
	mEq/24 hours		*μg/24 hours*	*kg*	*mEq/24 hours*		*mEq/L*
Normal Na$^+$							
L.I., 32-year-old male							
3/24	105	124		56.8	163	136	
3/25	105	124	123	56.8	144	93	
3/26	102	5		56.7	131	29	4.7
3/27	102	5		56.3	129	26	
3/28	102	5		55.4	88	25	
3/29	102	5		55.3	84	27	
3/30	102	5	112	55.5	73	24	3.9
3/31	102	5		55.5	79	21	
4/1	102	124	61	54.4	155	47	
4/2	102	124		54.4	124	49	3.7
Low Na$^+$							
JH, 23-year-old male							
Regular ward							
9/22			157		180	50	4.1
9/23	5	3		73.3	75	25	
9/24	5	3	760	72.5	18	21	
9/25	5	3		72.2	8	25	
9/26	5	3		71.7	6	20	
9/27	5	3		70.9	5	22	
9/28	5	3	460	71.3	2	13	3.2
9/29	5	3		70.8	0.6	11	
9/30	5	3	370	70.8	0.6	11	3.3

* U$_{Na}$$^+$V = urinary sodium excretion, and U$_K$$^+$V = urinary potassium excretion.
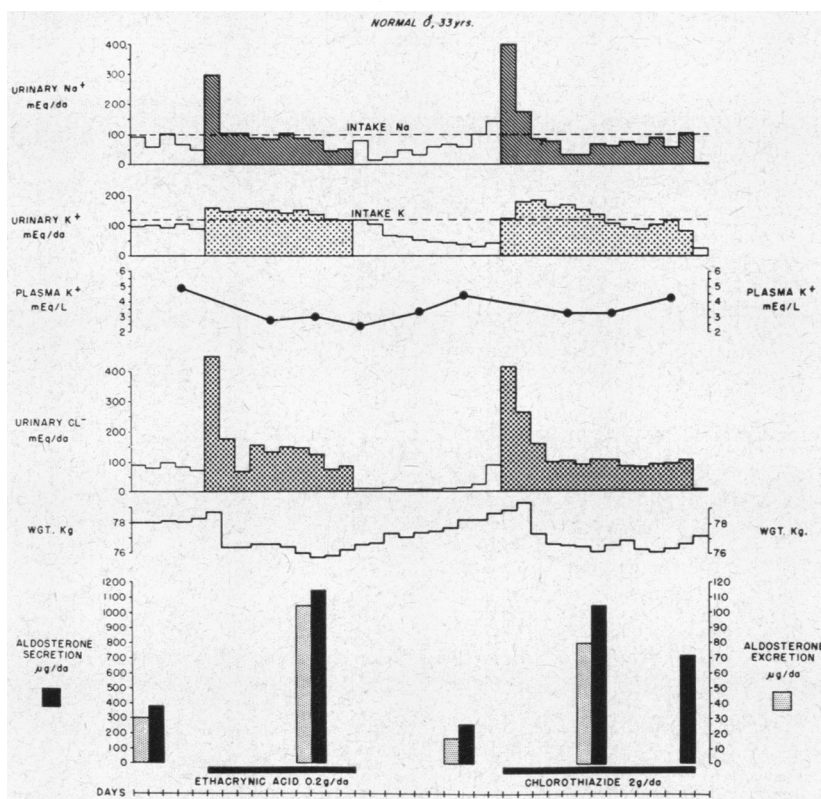
FIG. 4. EFFECT OF DIURETICS ON ELECTROLYTE BALANCE AND ALDOSTERONE SECRE-
TION. Both ethacrynic acid and chlorothiazide produced weight loss and increased
urinary excretion of sodium, potassium, and chloride. Despite negative potassium
balances and hypokalemia in both studies aldosterone secretion and excretion rose
to very high levels.

put in response to potassium administration was
observed after the disease process had progressed
from the advanced to the accelerated phase.

Aldosterone-secreting adenomas. In three pa-
tients in whom hypertension and hypokalemia were
caused by the presence of aldosterone-secreting
tumors, the administration of potassium produced
very large rises in aldosterone production (mean,
+ 1,303 μg per 24 hours). Two of these patients
received normal dietary sodium; one was salt de-
pleted. The secretion rate of one patient (BOR)
rose from 1,540 to 3,802 μg per 24 hours accom-
panied by a rise of only 1 mEq per L in plasma
K⁺ concentration. A detailed balance study of
another patient (Figure 5) illustrates the fall of
aldosterone secretion and plasma [K⁺] to control
values within 4 days after K⁺ administration was
discontinued.

*Potassium administration to patients with renal
tubular disease.* The effects of oral potassium sup-

plements before and after sodium depletion were
determined in extended balance studies of two
normotensive patients with renal tubular disease.

In both of these patients when potassium sup-
plements were added to a regular sodium diet
(75 to 105 mEq per 24 hours), very large in-
creases in aldosterone secretion rates above their
control values were observed (+ 336 and + 2,581
μg per 24 hours) (Figure 6). Although serum
K⁺ concentration rose, the absolute values never
exceeded the normal range.

Even greater rises in aldosterone secretion oc-
curred in response to potassium after sodium de-
pletion. In the patient with renal tubular acidosis
aldosterone output at first increased to 977 μg per
24 hours with sodium restriction despite concom-
itant hypokalemia; it then fell to 433 μg per 24
hours as renal K⁺ wastage continued. At this
point the addition of potassium supplements again
caused a sharp increase in aldosterone to 2,618 μg

TABLE III—*Effect of potassium administration upon the*

Patient	Date	Diet		Aldosterone		Weight	U~Na~+V	U~K~+V	Plasma [K+]
		Na+	K+	SR	ER				
		mEq/24 hours		*µg/24 hours*		*kg*	*mEq/24 hours*		*mEq/L*
Primary hypertension—uncomplicated									
ELL　38 N male	8/26	96	96	219		78.0	76	72	3.7
		KCl, 107 mEq orally per day for 5 days							
	8/31	96	203	191		77.6	62	184	4.0
		Stop KCl							
	9/2	96	96	168		77.2	60	82	3.5
GRA　28 N female	12/16	105	88	399		59.4	9	21	3.1
		KCl, 107 mEq orally per day for 5 days							
	12/22	105	190	311		61.2	104	189	4.5
	12/26	105	88	256		61.9	160	148	3.1
COR　53 W female	5/23	Regular Na—ward			24	53.4	67	57	4.3
		KCl, 107 mEq orally per day for 5 days							
	5/28	Regular Na—ward			32	53.2	67	142	4.3
MEY　41 W male	5/24	Regular Na—ward		339		72.0	70	54	3.7
		KCl, 5 g orally per day for 5 days							
	5/29	Regular Na—ward		402		72.2	53	148	4.2
LAC　47 W female	5/23	11	85	580		57.5	18	67	4.2
	5/25	11	85	550		57.1	12	70	
		KCl, 87 mEq for 1 day, 107 mEq orally per day for 8 days							
	5/30	11	192	850		56.9	4	127	4.2
DEC　39 W female	4/9	11	85	920		51.9	22	63	4.5
		KCl, 6 g orally per day for 3 days							
	4/13	11	85	1,440		50.6	12	116	4.3
Advanced hypertension									
SUC　44 W male	10/22	Regular Na—ward		552		65.8	127	71	3.5
		KCl, 107 mEq orally per day for 4 days							
	10/27	Regular Na—ward		818		66.4	60	122	3.8
GUN　31 N female	8/24	95	68	411		52.7	129	63	3.9
		KCl, 107 mEq orally per day for 6 days							
	8/26	95	175	821		52.3	127	146	5.6
	8/28	95	171	659		52.1	64	112	5.6
		Stop KCl							
	9/2	95	68	508		52.2	79	63	4.3
BUL　42 N female	10/11	100	63	295		64.1	135	57	4.1
		KCl, 107 mEq orally per day for 4 days							
	10/15	100	170	543		63.7	140	176	4.5
	10/22	11	88	572		62.7	8	55	4.3
		KCl, 107 mEq orally per day for 4 days							
	10/26	28	196	996		64.4	17	184	4.8
NOE　42 N female Premalignant	4/1	90	87	302		47.1	30	23	3.6
		KCl, 107 mEq orally per day for 5 days							
	4/6	90	194	1,086		48.0	66	195	5.6
		Stop KCl							
	4/10	90	87	318		48.7	60	66	
Malignant BP									
NOE　42 N female readmitted	11/20	90	86	747		51.6	88	58	2.8
		KCl, 107 mEq orally per day for 4 days							
	11/24	90	233	2,044			50	88	
WIG　44 W female	9/23	70	87	1,200		90.2	80	63	2.8
		KCl, 87 mEq orally per day for 7 days							
	10/8	65	156	2,700		88.1	42	44	5.2

* Abbreviations: SR = secretion rate; ER = excretion rate; BP = blood pressure.

*aldosterone secretion and excretion of patients with hypertension**

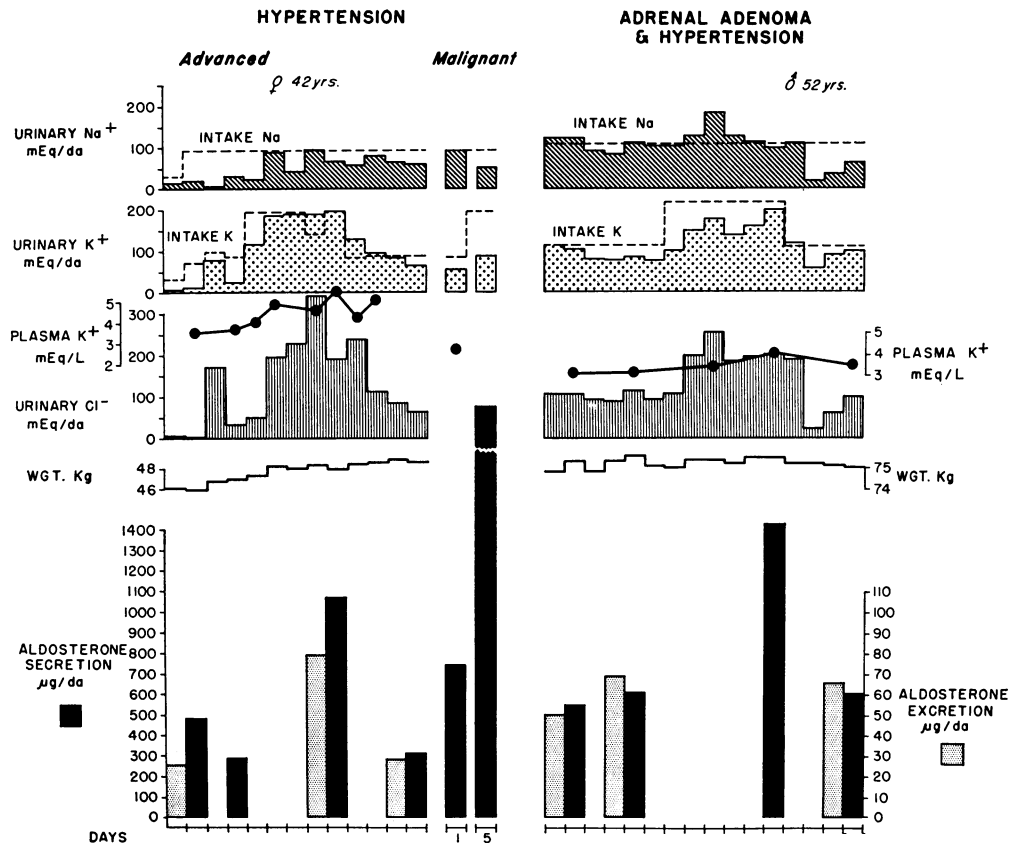| Patient	Date	Diet Na+	Diet K+	Aldosterone SR	Aldosterone ER	Weight	$U_{Na^+}V$	U_K^+V	Plasma [K+]
		mEq/24 hours		*µg/24 hours*		*kg*	*mEq/24 hours*		*mEq/L*
Hypertension secondary to unilateral renovascular disease									
CHA 58 W male	12/15	106	114	215		68.4	92	82	3.4
		KCl, 107 mEq for 4 days							
	12/19	106	221	449		68.4	124	200	3.8
WOH 39 W male	3/18	107	90	395		98.4	87	80	4.2
		KCl, 107 mEq for 5 days							
	3/24	107	197	505		97.0	99	174	5.3
		Stop KCl							
	3/27	107	90	303		96.2	61	84	3.9
CAC 46 W male	5/11	Ward constant Regular Na+		783		78.7	74	100	4.4
		KCl, 107 mEq for 5 days							
	5/16	Regular Na+—ward		1,948		77.5	85	228	5.5
		Stop KCl							
	5/19	Regular Na+—ward 104	103	986		77.4	68	132	5.2
		KCl, 107 mEq for 4 days							
	5/27	104	103	1,547		77.1	100	213	4.5
MAN 48 W male	10/7	82	95		14	73.5	67	85	4.7
		KCl, 107 mEq for 3 days							
	10/10	82	203		39	73.0	90	194	5.2
RYA 58 W male	1/1	Regular Na+—ward			38		42	62	3.4
		KCl, 107 mEq for 5 days							
	1/7	Regular Na+—ward			72		136	176	3.6
		Stop KCl							
	1/10				44		36	57	3.5
HOL 42 W male	7/26	97	63	112		45.3	73	34	3.8
		KCl, 107 mEq for 5 days							
	7/31	97	176	570		43.9	24	128	4.5
TOR 38 W male	8/31	95	76	462		47.3	78	60	3.6
	9/2	95	76	575		47.4	99	125	3.1
		KCl, 107 mEq for 5 days							
	9/7	95	183	1,040		47.0	117	216	4.2
		Stop KCl							
	9/9	95	76	625		47.2	64	92	4.0
		Readmitted with graft occluded; very high BP							
	10/9	94	95		50	41.3	145	115	2.8
	10/11	92	95		41	43.0	81	77	3.0
		KCl, 107 mEq for 4 days							
	10/14	92	200	1,340		42.4	101	138	2.8
	10/16	92	202	1,267		42.0	108	187	4.1
Adrenal adenoma and high BP (Conn's syndrome)									
WOR 52 W male	3/21	102	110	607		75.6	107	85	3.1
		KCl, 107 mEq orally per day for 6 days							
	3/28	102	219	1,432		75.0	98	199	4.0
		Stop KCl							
	4/1	102	110	602		75.0	62	110	3.5
BOR 33 W female	5/30	Regular Na+—ward		1,540		50.9	200	120	2.4
		KCl, 107 mEq orally per day for 11 days							
	6/10	Regular Na+—ward		3,802			130	317	3.4
MAR 60 W female	3/13	22	75	1,080		61.0	9	41	2.5
	3/20	158	75	650		61.6	54	29	
		KCl, 135 mEq orally per day for 13 days							
	3/22	12	185	750		61.3	87	52	
	3/31	13	210	1,900		61.9	63	190	4.5

FIG. 5. POTASSIUM ADMINISTRATION IN SEVERE HYPERTENSIVE DISEASE AND IN PRIMARY ALDOSTERONISM. In contrast to normal subjects, these patients when maintained on a normal sodium intake exhibited striking increases in aldosterone secretion in response to potassium administration. The phenomenon occurred without significant changes in sodium balance. Plasma potassium levels were increased but did not exceed the normal range.

per 24 hours. In the other patient with nephropathy sodium deprivation combined with potassium administration caused an enormous rise in the aldosterone secretion rate to values over 6,500 μg per 24 hours (Figure 6).

Discussion

The data demonstrate that potassium administration stimulates, and potassium depletion retards, aldosterone secretion in man. The findings are in harmony with earlier work in the dog (11, 16, 24, 25) and with the reports that potassium increases the excretion of a urinary metabolite of aldosterone in man (13–17).

The present study also points up three factors that can operate to amplify adrenal responsiveness to potassium administration. These are 1) the

state of sodium balance, 2) the presence of an ill-defined disturbance of renal function (that may have activated the renin-angiotensin system) as observed in the patients with renal arterial stenosis, advanced hypertensive disease, and renal tubular disorders, and 3) the presence of aldosterone-secreting adrenal tumors.

Potassium administration to normal subjects produced only modest increments in aldosterone secretion (mean, + 107 μg per day); the administration of similar amounts after sodium depletion caused marked increments in aldosterone secretion (mean, +841 μg per day). Qualitatively similar but smaller response patterns were observed in patients with essential hypertension. This modifying influence of the state of sodium balance on adrenal cortical responsiveness to potassium is opposite to that observed with infu-

sions of angiotensin II. Sodium depletion blunts both the pressor response and the adrenal secretory response to infused angiotensin (26, 27) possibly because higher circulating levels of endogenous renin and angiotensin render their target organs hyporesponsive to exogenous polypeptide.

In a group of 13 patients with renal arterial stenosis and advanced or malignant hypertension, in two patients with renal tubular disorders characterized by renal sodium wastage, and in three patients with primary hyperaldosteronism, the administration of similar amounts of potassium produced much greater increases in aldosterone secretion, even though these patients were receiving a normal sodium intake. In these various disorders

the mean increments ranged from a low of + 434 μg per day to a high of + 1,459 μg per day.

The means by which changes in potassium balance affect aldosterone secretion are still not entirely clear. It seems unlikely that potassium exerts its effect by modifying sodium and water balance because in the bulk of our studies neither the stimulating effect of potassium administration nor the retarding influence of potassium deprivation was associated with any consistent change in sodium balance or in weight (Figures 1 to 3, Tables I and II). It is true that urinary sodium excretion did rise slightly in a few subjects during potassium administration [Figures 1 (left) and 5 (right)]; however, other subjects in whom the
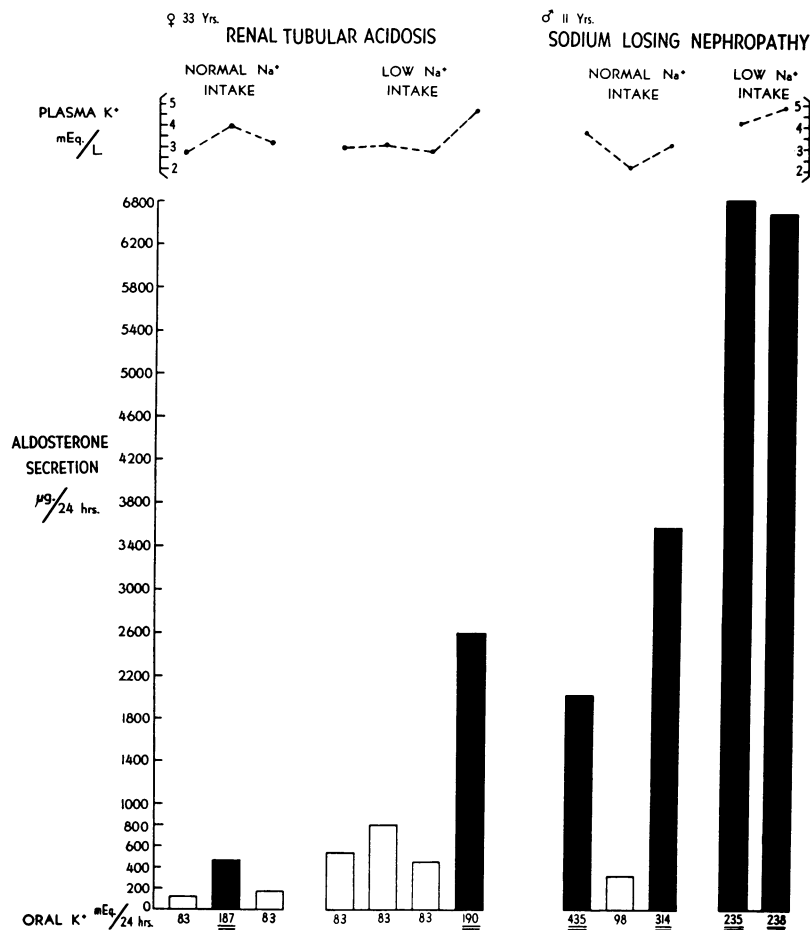

FIG. 6. EFFECT OF POTASSIUM ADMINISTRATION UPON ALDOSTERONE SECRETION OF TWO PATIENTS WITH RENAL TUBULAR DISEASE. Large changes in aldosterone secretion rate occurred in response to altered K+ balance when the patients received a normal sodium diet. A low sodium intake plus potassium induced extreme oversecretion of the hormone. In both, serum potassium concentration increased but did not exceed normal levels.
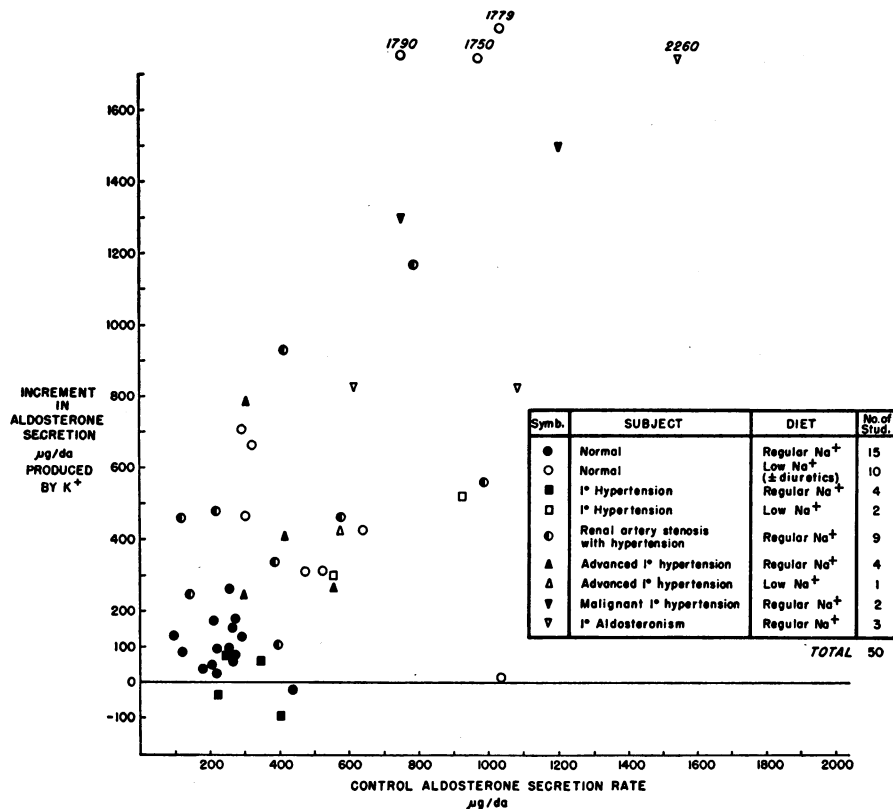
FIG. 7. EFFECT OF POTASSIUM SALT ADMINISTRATION ON ALDOSTERONE SECRETION IN 50 BALANCE STUDIES OF NORMAL SUBJECTS AND OF PATIENTS WITH HYPERTENSIVE DISEASES. The magnitude of the increments in aldosterone secretion induced by oral administration of 87 to 150 mEq per day of potassium appear directly related to the control rate of aldosterone secretion.

rise in aldosterone secretion induced by potassium was the same or much larger did not exhibit such a negative sodium balance [Figures 1 (right) and 5 (left)].

Potassium administration might operate indirectly to stimulate aldosterone secretion by activating the renin-angiotensin system or by enhancing the adrenotrophic action of available circulating angiotensin. Against the former possibility are preliminary observations (28) in six subjects of the present study which indicate that potassium-induced rises in aldosterone were not consistently accompanied by elevations of plasma renin activity. The latter idea is supported by the bulk of the present observations which indicate that the adrenal response to potassium is greatly enhanced in situations where plasma renin and angiotensin are likely to be increased (i.e., sodium depletion, renal disease, and advanced hypertensive disease)

(8–10). Against it, however, is the increased adrenal responsiveness to potassium observed in all three patients with primary aldosteronism, a situation where plasma renin activity is presumably very low (29).

Perfusion studies in dogs (12) and sheep (30) have shown that rather large changes in arterial plasma potassium levels can directly affect adrenal cortical activity. However, it may not be proper to explain the changes in aldosterone secretion observed in the present study solely in terms of alterations in plasma K^+ concentration. In a majority of situations (Tables I and III, Figures 1, 5, and 6) potassium administration caused large increases in aldosterone secretion, whereas plasma potassium levels remained within the normal range. Also, the induced increments in potassium concentration associated with the large increases in aldosterone secretion (salt-depleted normals, ad-

vanced hypertension, renal tubular disease) were no greater than the increments observed in the normal subjects who exhibited a minimal hormonal response to potassium salts. Lastly, the marked hypokalemia of diuretic therapy exerted less retarding influence on aldosterone secretion than the milder hypokalemia of dietary depletion. Therefore, it seems possible that the tissue uptake of potassium somewhere in the body (perhaps the adrenal glomerulosa cells), rather than the absolute level of plasma potassium, is the more critical determinant of the aldosterone response to alterations in potassium balance.

A relationship derived from the present data may improve our understanding of how potassium ions affect the adrenal cortex. The magnitude of the response of the adrenal glomerulosa to potassium observed in 50 studies of normal and hypertensive subjects was found to be directly related to the prior rate of production of aldosterone (Figure 7), that is, larger increments in aldosterone secretion were induced by potassium when the adrenal gland was already hyperactive. This relationship held whether adrenal overactivity resulted from an autonomous adenoma or from presumed extra-adrenal stimulation via renin (sodium depletion, diuretics, hypertensive-renal disease).

Thus, all of our results might best be explained by postulating that 1) adrenal cellular accumulation of potassium in response to a positive K^+ balance directly increases aldosterone secretion, and 2) the effect of a given amount of potassium upon adrenal production of aldosterone is directly related to the pre-existing level of adrenal stimulation by other factors. The other known factors that might operate to condition the effect of potassium on the adrenal are the level of circulating renin and angiotensin as affected by changes in sodium balance or as altered by renal dysfunction in the patients with hypertension or renal diseases, conceivably ACTH release in acute stress situations, and primary or autonomous adrenal hyperactivity as encountered in patients with adrenal tumors.

These findings complicate current concepts of the control of aldosterone and electrolyte homeostasis. They imply that there may be a double cycle feedback system whereby primary control of aldosterone secretion by the renin-angiotensin system responsive to changes in sodium balance or renal blood flow or both is supplemented and

complemented by another mechanism in which a direct stimulatory effect of potassium upon the adrenal gland is conditioned by the existing level of adrenal secretory activity. Such a dual mechanism would provide a finely adjustable homeostatic defense of plasma K^+ concentration in the event of renal failure or in the face of any large or sudden change in potassium balance.

Summary

Dietary potassium supplements (107 to 160 mEq daily for 4 to 6 days) stimulated aldosterone secretion in 23 of 25 studies of normal subjects and in 24 of 26 studies of patients with hypertensive or renal tubular disease. Dietary or diuretic-induced potassium depletion reduced aldosterone secretion if simultaneous sodium depletion was avoided but did not prevent an aldosterone rise in response to renal sodium loss. The influence of potassium depletion on aldosterone secretion could not be exclusively related to plasma potassium levels because the more severe hypokalemia of diuretic therapy was accompanied by an increased, and the milder hypokalemia of dietary depletion by a reduced, aldosterone secretion.

The effect of potassium balance on aldosterone secretion could not be explained adequately by induced changes in sodium balance and activation of the renin-angiotensin system or even by observed alterations in plasma potassium levels. It may therefore result from a more subtle consequence of altered potassium balance, perhaps involving direct adrenal cellular uptake of potassium.

The aldosterone secretory response to potassium administration was enhanced by four- to tenfold or more 1) after sodium depletion in normal subjects or patients with essential hypertension, 2) in patients receiving normal sodium diets who had renal arterial stenosis, advanced or malignant hypertension, or renal tubular disease characterized by sodium wasting, and 3) in patients with primary aldosteronism. In these circumstances, the magnitude of the aldosterone response to potassium was equal to or greater than that described for angiotensin. In normal subjects and in hypertensive patients with primary or secondary aldosteronism, the aldosterone response to potassium was directly related to the pre-existing rate of aldosterone secretion, regardless of whether the

latter resulted from an autonomous tumor or from extra-adrenal stimulation, presumably via renin.

This conditioning of the stimulatory influence of potassium upon aldosterone by the prior level of adrenal activity suggests that the regulation of aldosterone is normally controlled by a complementary interrelationship between direct adenotrophic effects of potassium and activity of the renin-angiotensin system.

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