The Effect of Potassium Loading on Sodium Excretion and Plasma Renin Activity in Addisonian Man

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ABSTRACT Potassium has been shown to suppress plasma renin activity (PRA). This study was designed to study the role of increased aldosterone production in the mediation of such a response. Five patients with adrenal insufficiency were placed on a diet of 60 meq potassium and 100–150 meq of sodium while receiving a constant amount of cortisone acetate and Florinef. Upright PRA was determined each day for 2–3 days in the control period and then for 3–4 days after potassium intake had been increased to 200–300 meq/day.

Potassium loading induced a natriuresis. Hence, patients were either sodium replaced (six studies in four patients) or allowed to become sodium depleted (three patients). Potassium loading without replacement was associated with a decrease in weight, negative sodium balance, hyperkalemia, and a positive potassium balance. PRA rose during the experimental period. Potassium loading with sodium replacement was associated with little change in weight or sodium balance. Hyperkalemia and positive potassium balance were present to the same degree as found in the studies without sodium replacement. When all PRA values are considered (both morning and evening values) there was no significant change with potassium loading (+ 1.31 ng/ml per h; range + 6.9 to − 2.0). We conclude that hyperkalemia or a positive potassium balance did not suppress PRA in Addisonian man in these studies when sodium balance was maintained, nor did it prevent a rise in PRA when sodium balance was negative.

INTRODUCTION

Recent studies have demonstrated that potassium may play an important role in the regulation of renin secretion. Acute KCl infusions into the renal artery or systemic circulation have been shown to suppress renin secretion in both experimental animals and man (1–6). Chronic potassium administration has also been shown to suppress renin values (7–10). Since potassium loading stimulates aldosterone secretion, it is not clear whether the observed renin suppression is a direct potassium effect or is secondary to the rise in aldosterone. Therefore, we studied the effect of potassium loading in adrenalectomized patients and in patients with primary adrenal insufficiency while on a daily, fixed dose of exogenous mineralocorticoid. Our results show that hyperkalemia and/or a positive potassium balance does not directly result in suppression of peripheral plasma renin activity (PRA)[1] in these subjects.

METHODS

Three bilaterally adrenalectomized patients (P. H., C. D., and M. W.) and two patients with idiopathic primary adrenal insufficiency (D. B. and C. C.) were studied at the Clinical Research Center. Each patient was maintained on 25 mg of cortisone acetate and 0.1 mg Florinef (fludrocortisone acetate, E. R. Squibb and Sons, New York) in the morning and 12.5 mg cortisone acetate and 0.1 mg Florinef in the evening. The patients were kept on a constant dietary sodium intake from 80 to 150 meq per day, individually selected to approximate their previously determined base-line urine sodium excretion, while receiving a constant potassium intake of 60 meq per day. After sodium balance or stable body weights were achieved, morning and evening upright PRA and serum electrolytes were measured each day for 3–4 days after the patients had been walking for 1 h. While the sodium intake remained constant, the dietary potassium intake was then increased to 200 or 300 meq per day with repeat measurements of the PRA, serum and urine electrolytes,[2] and morning body weights for 3–4 days.

[2] Stool electrolytes were not measured. Each patient had only one normal bowel movement per day. Potassium balance used here represents the difference between potassium intake and urine potassium excretion.

TABLE I
Potassium Loading with and without Sodium Replacement

Patient	Weight change K loading	Na+ balance K loading	K+ balance K loading	Mean serum K Con-trol	Mean serum K K loading	Mean PRA* Control	Mean PRA* K loading	Last day PRA‡ Control	Last day PRA‡ K loading
	kg	*meq*	*meq*	*meq/liter*	*meq/liter*	*ng/ml/h*	*ng/ml/h*	*ng/ml/h*	*ng/ml/h*
Without sodium replacement									
C. D.	−2.4	−167	+126	4.2	5.0	6.3	7.4	4.4	12.7
D. B.	−0.8	−203	+107	4.5	5.5	6.1	50.3	5.1	79.5
M. W.	−1.5	−450	+247	4.2	5.5	9.9	23.3	11.7	38.8
Mean	−1.6	−273	+160	4.1	5.3	7.4	21.0	7.1	43.6
SE						1.2	12.5	2.3	19.4
t							1.6		1.9
With sodium replacement									
C. D. no. 1	−0.1	−3	+79	4.6	5.3	8.2§	6.4	8.2§	6.2
C. D. no. 2	+0.5	−14	+159	4.4	5.2	3.9	3.2	4.6	5.4
P. H.	+0.2	+14	+226	5.0	6.2	15.4	17.3	11.5	20.1
C. C. no. 1	−0.2	+84	+64	5.0	5.8	163.3	194.3	260.0	260.0
C. C. no. 2	−0.3	+61	+112	4.6	5.9	77.5	131.5	60.0	125.0
M. W.	−2.2	+25	+165	4.2	5.4	1.3	3.2	1.5	6.3
Mean	−0.4	+28	+134	4.6	5.6	7.2‖	7.5‖	6.5‖	9.5‖
SE						3.0	3.3	2.1	3.5
t							0.07		0.7

* Mean of 11 a.m. renin values.
‡ PRA at the end of the control period and at the end of potassium loading.
§ Single day value (last day of pre-K loading).
‖ Values of C. C. are excluded from the means and SE because of the high and variable PRA values.

Potassium loading was accompanied by a natriuresis. Hence, patients either had sodium replacement equivalent to the excess urinary sodium (six studies in four patients) or were allowed to become sodium depleted (three studies in three patients). Sodium replacement was carried out as follows: Urinary sodium excretion was determined in 8-h periods. The excess sodium (above base line) excreted in each period was given orally as table salt during the next 8-h period.

Peripheral venous blood was collected in iced tubes containing powdered EDTA and immediately spun down in a refrigerated centrifuge at 3,000 rpm for 20 min at +4°C. The supernate was then pipetted off and frozen at −15°C until the determination of the renin activity. PRA was measured using a radioimmunoassay of generated angiotensin I (11–12). Specimens were assayed in triplicate and in dilutions so that all specimens were assayed on the most precise portion of the standard curve. Results are expressed as ng angiotensin I/ml per h for specimens incubated at pH 5.5. Normal values for this assay have been previously published (normal values, 7.7±4.6 for upright values on 120 meq sodium intake; 17.2±10.1 for upright values on 10 meq sodium intake).

RESULTS

Potassium loading without sodium replacement. Table I shows the data on the three studies in three patients who were potassium loaded, manifested a natriuresis, and did not have urine sodium replaced. Potas-

sium loading was accompanied by a decrease in body weight and a mean negative sodium balance of 273 meq during the potassium loading period. Potassium balance was positive during the potassium loading period, and the serum potassium rose to a mean level of 5.3 meq/liter. The 11 a.m. PRA during the control period was normal in all three patients and progressively increased during the potassium loading period in two of the three patients. When the mean of the PRA values from the last day of the control period was compared to that of the last day of potassium loading, the *t* value was 1.9. Hence, potassium loading with a positive potassium balance and hyperkalemia did not suppress PRA in any patient, nor did it prevent a rise when body sodium balance became negative.

Fig. 1 is a representative graph of the daily balance data in one patient, while Table II shows the individual daily balance data in all three patients. In two patients (D. B. and M. W.) there was a progressive rise in the PRA throughout the potassium loading period while an increase in PRA in C. D. was only seen on the last day. The peak PRA in C. D. after potassium loading was 12.7 ng/ml per h, considerably less than that of D. B. (79.5 ng/ml per h) and of M. W. (38.8 ng/ml per h). All patients had a negative sodium balance,

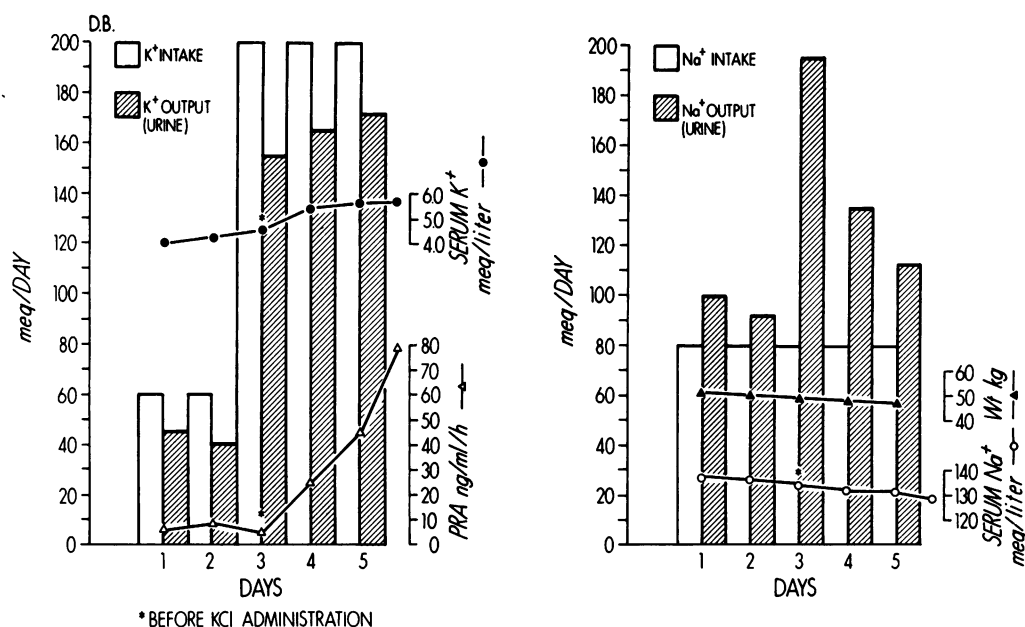K^+ *Loading,* Na^+ *Excretion, and PRA in Addisonian Man*   347

FIGURE 1 Daily sodium and potassium balance data, weight, serum electrolytes, and PRA changes before and during the potassium loading period on one patient (D. B.) who did not have urine sodium replaced.

positive potassium balance, and a comparable serum potassium rise during the potassium loading period. However, C. D. was the only subject whose sodium balance was positive during the prepotassium loading and his net sodium balance for the entire experimental period was only — 20 meq. Thus the state of the prepo-

TABLE II

Individual Daily Balance Data in Patients C. D., D. B., and M. W.

| Patient	Day	Na_I	Na_U	Serum Na	8 a.m. weight	K_I	K_U	Serum K 11 a.m.	PRA 11 a.m.
		meq/day	meq/day	meq/liter	kg	meq/day	meq/day	meq/liter	ng/ml/h
C. D.	1	150	128	140	68.1	60	51	4.2	8.8
	2	150	85	139	68.1	60	40	4.3	6.2
	3	150	104	141	68.2	60	47	4.1	5.9
	4	150	191	138*	68.2*	200	111	4.5*	4.4*
	5	150	199	138	67.9	200	123	4.6	3.8
	6	150	219	133	67.3	240	288	4.8	6.3
	7	150	158	137	66.7	240	232	5.5	7.0
	8			136	65.8			5.4	12.7
D. B.	1	80	103	138	50.7	60	47	4.0	6.0
	2	80	92	138	49.8	60	40	4.1	7.3
	3	80	195	134*	49.5*	200	155	4.3*	5.1*
	4	80	136	131	49.1	200	167	5.6	25.5
	5	80	112	129	48.9	200	171	6.1	46.0
	6			129	48.7			6.3	79.5
M. W.	1	120	250	139	86.9	70	70	4.1	8.1
	2	120	309	140*	86.3*	220	110	4.2*	11.7*
	3	120	278	140	85.6	220	153	5.4	12.4
	4	120	221	138	85.3	200	150	6.4	18.8
	5			139	84.8			5.8	38.8

* Before KCL administration.
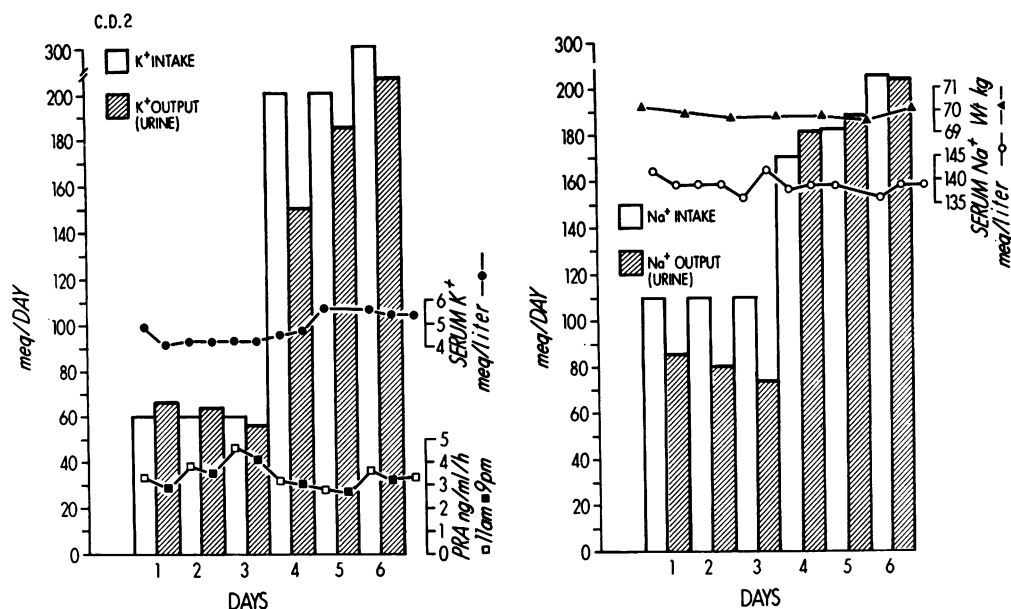
FIGURE 2 Daily sodium and potassium balance data, weight, serum electrolytes, and PRA changes before and during the potassium loading period on one patient (C. D. 2) in whom urinary sodium loss was replaced.

tassium loading sodium balance may have been an important factor in modifying the course of the renin values determined during potassium loading and only when natriuresis results in subnormal body sodium content may one expect a rise in PRA to occur.

Potassium loading with sodium replacement. Table I also shows the cumulative data on the six studies in four patients in whom the sodium loss during the potassium loading period was replaced every 8 h. Potassium loading was accompanied by little change in body weight or sodium balance during the potassium loading period (mean, + 28 meq). However, the mean positive potassium balance and the serum potassium during the potassium loading period were + 134 meq and 5.6 meq/ liter, respectively. In four of the studies the PRA did not change when comparing either the mean or the last day values of the control and potassium loading periods. Two of the studies in one patient, C. C., showed a rise in the mean PRA with potassium loading (31.0 and 54.0 ng/ml per h).

Fig. 2 and 3 are two representative graphs of the daily data in two of the studies in two patients, while the individual daily balance data for these six studies are shown in Table III. It is apparent that hyperkalemia and/or a positive potassium balance did not suppress the PRA despite a small positive sodium balance in four of the six studies. In addition the diurnal variation that is normally observed in the PRA (13) was not altered. The PRA values were extremely high in C. C. and showed wide fluctuations in both the 11 a.m. values and

in the diurnal variations recorded, even though there was little apparent difference in sodium or potassium balance during the prepotassium or potassium loading periods or changes in body weight or serum potassium when compared to the other patients. The only explanation we have is that she was a newly diagnosed primary Addisonian patient who was started on her glucocorticoid and mineralocorticoid replacement just several days before the initiation of her first study. She may have still been volume depleted although there was no orthostatic pulse or blood pressure change. Despite these wide fluctuations in her PRA, the combined morning and evening mean PRA showed little difference in the first study (+ 0.9 ng/ml per h) or in the second (+ 6.9 ng/ ml per h) when comparing the prepotassium loading to the potassium loading periods. In addition, no 11 a.m. PRA during the potassium loading period was lower than the lowest 11 a.m. PRA value in the control prepotassium loading period. Hence, even in this patient with wide PRA fluctuation, hyperkalemia, and/or a positive potassium balance did not suppress the PRA.

Finally, comment should be made on the observed weight loss seen in M. W. during the prepotassium and potassium loading periods both with and without sodium replacement. During the study with no sodium replacement the weight loss is perhaps commensurate with extracellular fluid loss and consistent with the rather elevated base-line renin values. During the second experiment the weight loss could not be correlated with the slightly positive sodium balance or the low base-line

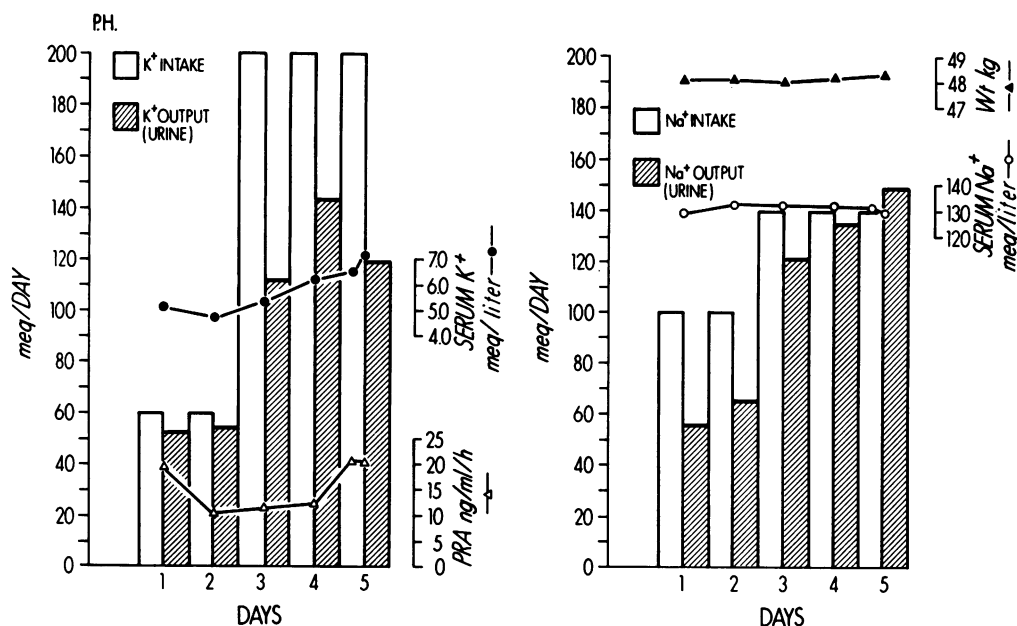*K⁺ Loading, Na⁺ Excretion, and PRA in Addisonian Man* 349

FIGURE 3 Daily sodium and potassium balance data, weight, serum electrolytes, and PRA changes before and during the potassium loading period on one patient (P. H.) in whom urinary sodium loss was replaced.

renin values. This patient was extremely obese and had been placed on a 1,200 calorie diet during this time. Thus, we have attributed this weight loss to caloric deficit and loss of body tissue.

DISCUSSION

Acute and chronic potassium administration in normal subjects results in depression of PRA. The data obtained in experimental animals and human beings with chronic potassium administration has generally been felt to indicate a direct effect of potassium on PRA (6–10). In two of these studies (9–10) an increase in aldosterone secretion rate has been shown, presumably due to the known effect of hyperkalemia or positive potassium balance on aldosterone (3, 14–19). However, renin suppression was not thought to be due to sodium retention since sodium intake was restricted. Recent data, however, do suggest that a small (20 meq) positive sodium balance can acutely result in suppression of renin activity (20). Furthermore, the possibility exists that some aldosterone mediated event other than body sodium retention might result in suppression of PRA. The present study was designed to evaluate the role of mineralocorticoid hormones in the plasma renin response to potassium loading. While not supplying the answer of how an increase in aldosterone suppresses renin, our data do demonstrate the essential role of high mineralocorticoid levels in this event. The PRA in our subjects responds appropriately to change in body sodium even during potassium loading.

Studies of acute potassium infusion may have some relevance to our data. Shade, Davis, Johnson, and Witty (4) infused potassium chloride into the renal artery of dogs and found a decrease in renin activity only with the filtering model. In these and other acute potassium loading studies renin suppression (1, 2, 5) as well as natriuresis (1, 2, 4–6, 21) was confined to the ipsilateral kidney. Neither alteration of renal hemodynamics (2–5) nor direct mineralocorticoid effect (22) could be found responsible for the renin effect. Several observations indicate that potassium inhibits tubular reabsorption of sodium proximal to the distal tubule (5, 23, 24), and it has been proposed that the inhibition of renin secretion is secondary to an increase in the uptake of this excess sodium that is delivered to the macula densa (25, 26), although other investigators offer conflicting data concerning this (27–29). While the aldosterone secretion rate has been demonstrated to increase acutely with potassium administration, its role in the suppression of renin activity in acute studies (30, 31) remains unknown. It is well known that demonstrable effect on sodium transport lags behind aldosterone administration or secretion. In general, mediation of sodium (32) and potassium (33) transport is thought to require protein synthesis which requires at least an hour in the toad bladder assay system (32, 33) and perhaps much longer in mammalian kidney (34). However, aldosterone action independent of nucleic acid synthesis, which has been demonstrated in eryth-

TABLE III
Potassium Loading with Sodium Replacement

Patient	Day	Na$_I$	Na$_U$	Serum Na	8 a.m. weight	K$_I$	K$_U$	Serum K 11 a.m.	Serum K 10 p.m.	PRA 11 a.m.	PRA 10 p.m.
		meq/day	*meq/day*	*meq/liter*	*kg*	*meq/day*	*meq/day*	*meq/liter*		*ng/ml/h*	
C. D. no. 1	1	150	130	138*	66.0*	60	75	4.5*		8.2*	
	2	150	146	138	66.0	200	176	5.8		5.9	
	3	250	248	137	66.0	200	155	5.6		7.2	
	4	183	194	136	65.9	200	194	5.2	4.8	6.5	5.8
	5	180	178	137	65.9	200	196	5.5	5.2	6.2	5.7
C. D. no. 2	1	110	85	142	70.1	60	67	4.9	4.1	3.4	2.7
	2	110	80	138	69.9	60	64	4.3	4.3	3.8	3.5
	3	110	75	136*	69.7*	60	56	4.3*	4.3	4.6*	4.1
	4	170	181	138	69.7	200	150	4.5	4.7	3.1	3.0
	5	184	187	139	69.7	200	185	5.7		2.8	2.7
	6	205	205	136	69.6	300	206	5.6	5.4	3.6	3.1
	7			139	70.2			5.4		3.2	
P. H.	1	100	55	130	48.1	60	53	5.1		19.4	
	2	100	65	132*	48.1*	60	54	4.7*		11.5*	
	3	140	122	132	48.0	200	112	5.3		12.8	
	4	140	135	132	48.2	200	143	6.2		14.5	
	5	140	149	129	48.3	200	119	7.2		20.1	
C. C. no. 1	1	100	138	135	45.0	60	52	4.8		80.0	
	2	100	102	135	45.0	60	42			150.0	
	3	234	220	134*	44.8*	200	142	5.3*		260.0*	
	4	290	228	132	44.6	200	198	6.2	5.6	144.0	80.0
	5	240	238	129	44.6	200	196	6.0	7.2	180.0	
	6									260.0	
C. C. no. 2	1	150	122	138	44.7	60	48	4.6		76.0	
	2	150	138	136	45.0	60	55	4.6		112.0	
	3	220	200	138*	44.8*	200	148	4.6*		60.0	40.0
	4	195	160	136	44.5	200	144	5.0	7.0	137.0	58.0
	5	200	194	138	44.5	200	196	5.6		125.0	
M. W.	1	100	93	139	89.4	60	41	3.9	4.4	1.2	
	2	100	68	139	89.0	60	35	4.0	4.3	1.1	0.8
	3	100	77	139	88.8	60	30	4.1	4.3	1.6	0.9
	4	100	68	139*	88.4*	60	31	4.2*		1.2*	1.2
	5	150	158	137	88.0	200	128	4.8	5.3	1.1	1.4
	6	251	245	140	87.1	200	148	5.4	5.6	2.5	2.5
	7	227	200	139	86.5	200	159	5.1	5.9	2.8	4.2
	8			136	86.2			6.0		6.3	

* These values were determined before KCL administration. In all the above experiments except those on C. C., KCL administration was started at 8 a.m., thus the last control value for PRA occurs on the day before K administration. In C. C., K administration was started after the 11 a.m. samples were drawn on the 1st day of the experimental period of K loading.

rocytes (35), might acutely influence sodium transport with resultant decrease in renin release.

The natriuresis which was consistently seen in our Addisonian subjects with chronic potassium loading seems to be distinctively related to the presence of adrenal insufficiency on fixed mineralocorticoid replacement. Normal potassium loaded subjects have little sodium loss (9, 16, 36). In addition to aldosterone dependent sodium-potassium ATPase (33, 34), a potassium stimulated renal medullary sodium-potassium ATPase activity is known to exist (37). However, Silva, Hayslett, and Epstein (37) have shown that this activity is the same whether or not adrenal glands are intact. Thus our data suggest that an increase in aldosterone secre-

tion, which has time to exert its maximum metabolic effect, is necesssary for the maintenance of sodium homeostasis.

Our observations provide provocative information concerning the relationship of the sodium and potassium ion and the renin aldosterone system in man. If we assume that the marked natriuresis seen in our subjects resulted from inhibition of proximal sodium reabsorption, then enhanced distal tubule sodium delivery was present but there was no suppression of PRA as one would expect in intact subjects. The missing link in our patients was their inability to respond to potassium administration with increased aldosterone secretion. Our patients were on a mineralocorticoid replacement. Florinef, at the dose used in this study was certainly not adequate to prevent natriuresis from potassium loading and would appear inadequate to allow enough sodium transport to suppress renin release, even though this was the replacement dose usually used in clinical medicine. (The comparative potency of Florinef to aldosterone is 2:3 [38], and the average 24-h aldosterone secretion rate is usually 100–500 µg/day on a normal sodium-potassium diet [16, 39, 40] which is equivalent to 0.15 mg of Florinef.) Chronic potassium loading in man with 200 meq/day normally results in a two–fourfold increase in aldosterone secretion (16, 39, 40) which is comparably greater than the dose of mineralocorticoid used for replacement therapy in this study. Also, there might be sufficient difference between the structures of aldosterone and Florinef, such that Florinef might not have the same effect on sodium uptake and renin release. Further study is needed to define the interrelationship of renal tubular sodium flow, transport of sodium in the macula densa, and renin release, as well as the possible modifying role of aldosterone in this system. Our studies do confirm the well known inability of Addisonian man to tolerate potassium loading and suggest that high doses of aldosterone are necessary to combat the effect of potassium administration including the potassium-induced natriuresis.

ACKNOWLEDGMENTS

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