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THE NATURE OF THE ACTION OF INTRAVENOUS ALDOSTERONE:
EVIDENCE FOR A ROLE OF THE HORMONE IN
URINARY DILUTION *

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Aldosterone increases the renal retention of sodium chloride and promotes the excretion of potassium ions (1-11); but where and how the hormone acts in the renal tubule is poorly understood. The present study was designed to characterize further the mode and site of action of aldosterone in the nephron.

Information can be obtained about the site of action of a compound by observing its effect on free water formation (12). According to a current concept of renal physiology (13), reabsorption of solute (sodium chloride) is isosmotic in the proximal tubule (14), whereas, in the more distal segments, reabsorption may or may not be isosmotic (15, 16). During water diuresis (absence of antidiuretic hormone) the distal reabsorption of solute is selective, i.e., occurs without isosmotic amounts of water, leaving "solute-free" water behind for excretion (17). Thus, by determining the effect of a compound on solute excretion and on free water formation during maintained water diuresis, information may be obtained about its site of action (12). If aldosterone were to act to promote isosmotic reabsorption of sodium, the consequent reduction in solute excretion would be accompanied by a fall in urine flow and no change or fall in free water excretion. However, if aldosterone acts only at a more distal site, where reabsorption is selective, the reduced sodium excretion would be accompanied by no change in urine flow and hence, by a rise in free water excretion.

In the present study it has been shown that aldosterone can promote abstraction of sodium chloride exclusive of water from the tubular urine.

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This action takes place in the tubule at a locus distal to that of isosmotic reabsorption. Also, this effect of the hormone on sodium chloride reabsorption appears to be dissociated from the effect on potassium excretion.

EXPERIMENTAL

Seven studies were performed on 3 subjects without evidence of renal or cardiovascular disease. Four of the experiments were done with subjects maintained on a normal NaCl intake (4 to 6 g NaCl per day for 7 days), two with the subjects on a higher intake of salt for 7 days (8 to 20 g NaCl per day), and one after drastic salt deprivation (less than 250 mg per day for 6 days). In two subjects on normal salt intake, control studies of similar protocol but without administration of aldosterone were performed. All experiments were conducted in the fasting state at the same early morning hour with the subjects in a recumbent position.

Water diuresis was induced by having the patient ingest about 1,500 ml of water by mouth during the hour before the experiment and was subsequently maintained by intravenous infusion of 5 per cent dextrose and water at a constant rate, at least 2 ml per minute greater than urinary output. Adequate control periods were obtained until a steady state of maximum urine flow was demonstrated, so that any subsequent change in free water clearance could not be attributed to an increasing water diuresis.

When a steady state of maximum water diuresis had been achieved, 1 mg of *d,l*-aldosterone monoacetate in 10 ml of 10 per cent ethanol was administered intravenously.¹ This was followed by another 1 mg given in the dextrose and water infusion over the next hour. After the aldosterone administration was complete, the infusion of dextrose and water was continued at a constant rate.

Blood samples were taken via an indwelling heparinized needle and urine collections were made with an indwelling catheter except in Subjects S.H. and M.U., young males in whom adequate voluntary bladder emptying was possible at high rates of urine flow.

¹ *d,l*-Aldosterone monoacetate, 1,000 µg equivalent to 500 µg active *d*-aldosterone supplied by Ciba Pharmaceutical Products, Summit, N. J.

TABLE I
Detailed protocol of a typical experiment *

Time min	C _{PAH} ml/min	C _{in} ml/min	V ml/min	U _{osm} μOsm/ml	C _{osm} ml/min	C _{iso} ml/min	U _{NaV} μEq/min	U _{ClV} μEq/min	U _{KV} μEq/min	pH	Osm μOsm/ml	Plasma		
												Na μEq/ml	K μEq/ml	Cl μEq/ml
-150	635	148	18.3	54	3.5	14.7	135	100	35	5.65	283	136	4.7	97
-113	612	131	18.5	52	3.4	15.0	150	91	54	5.8				
-110	Inulin and PAH prime and start infusion of inulin and PAH in 5% dextrose and water at 20 ml/min.													
-78 to -29	635	148	18.3	54	3.5	14.7	135	100	35	5.65	281	136	3.8	98
-29 to -8	612	131	18.5	52	3.4	15.0	150	91	54	5.8				
0	1 mg d,l-Aldosterone given intravenously and 1 mg added to 1L of dextrose and water infusion.													
-8 to +21	637	137	17.3	46	2.9	14.5	163	118	80	5.75	273	134	3.6	97
+21 to +50	657	148	17.8	35	2.2	15.6	157	110	69					
+50	Aldosterone infusion completed; dextrose and water continued at 20 ml/min.													
+80 to +80	640	151	18.5	33	2.2	16.3	109	70	104	5.75	272	131	3.6	96
+80 to +110	646	141	18.0	31	2.0	16.0	83	54	86	5.5				
+110 to +139	633	155	18.5	30	2.0	16.5	48	46	61	5.3				
+139 to +168			17.9	30	2.0	15.9	57	47	77	5.4	270	128	3.7	93
+168 to +200	633	140	17.2	26	1.6	15.6	43	43	65	5.35				
+200 to +262			18.4	19	1.3	17.1	70	61	57		268	128	3.7	94
+212	Dextrose and water infusion stopped.													
+262 to +322			18.4	20	1.4	17.0	52	75	35					
+322 to +367			19.2	18	1.3	17.9	63	77	60					
+367 to +442			18.9	22	1.5	17.4	64	77	28					
+442 to +487			18.7	26	1.8	16.6	101	62	32					
+487 to +577			18.3	40	2.7	15.6	157	46	48					
+577 to +650			18.2	46	3.1	15.1	142	64	58					

* Subject S.H., 72.5 kg male on constant 6 g NaCl intake; 2,000 ml H₂O given p.o. at 6 a.m.

Plasma and urine samples were analyzed for inulin or creatinine, para-aminohippuric acid, and sodium, potassium and chloride, by methods previously described (12). The urinary pH was measured by a Beckman pH meter on freshly voided samples and the urine and plasma urea concentrations were determined by a modification of the urease method of Van Slyke and Cullen (18). The urine and plasma total solute concentration was measured with a Fiske osmometer.

Calculations. As indicated by Smith (13) and by Wesson and Anslow (17), urine can be divided into two moieties: the osmolar clearance (C_{osm}), the volume of water necessary to contain the urinary solutes in a solution isosmotic with the plasma ($C_{osm} = UV_{osm}/P_{osm}$); and the free water clearance (C_{H_2O}), the net excess or deficit of water beyond the osmolar clearance. During water diuresis the free water clearance is a positive value and is calculated as $C_{H_2O} = V - U_{osm}V/P_{osm}$, where V is the urine flow in milliliters per minute and U_{osm} and P_{osm} are the solute concentrations of urine and of plasma in milliosmoles per kilogram of water.

RESULTS

The results of these experiments are summarized in Tables I, II and III and in Figures 1 through 4. In Table III, a typical control protocol is given. In Table I the complete protocol of one experiment is given, and in Figure 1 the com-

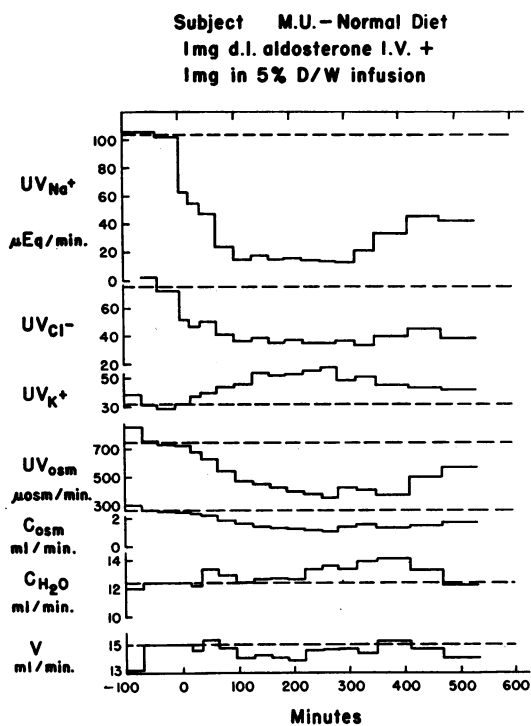


FIG. 1. GRAPH OF THE RESULTS OF A REPRESENTATIVE CLEARANCE STUDY (SEE TEXT).

TABLE II
Effect of intravenous aldosterone on electrolyte, solute and water excretion during maintained water diuresis *

Patient	Period	GFR	RPF	U _{NaV}	U _{KV}	U _{ClV}	pH	P _{osm}	U _{osm}	V	C _{osm}	C _{H₂O}
		ml/min	ml/min	μEq/min	μEq/min	μEq/min		μOsm/ml	μOsm/ml	ml/min	ml/min	ml/min
S.H. (normal diet)	Control	C _{In} 139	C _{PAH} 623	150	54	91	5.80	281	52	18.5	3.4	15.0
	Aldo	C _{In} 140	C _{PAH} 633	52	35	75	5.35	268	19	18.4	1.4	17.0
M.U. (normal diet)	Control			104	30	77.3	6.40	290	50	15.0	2.6	12.4
	Aldo			14	53	36.4	6.10	286	26	14.9	1.3	13.6
M.U. (8 g NaCl in daily diet)	Control	C _{In} 114	C _{PAH} 620	91	39	33		271	46	13.9	2.4	11.5
	Aldo	C _{In} 115	C _{PAH} 573	32	60	19		270	23	14.0	1.2	12.8
J.O. (low NaCl diet)	Control	C _{Cr} 196		257	131	288		291	45	33.5	5.1	28.3
	Aldo	C _{Cr} 200		156	110	188		282	18	31.3	2.0	29.4
J.O. (8 g NaCl in daily diet)	Control	C _{Cr} 204		714	67	1,155		277	89	45.0	14.8	31.0
	Aldo	C _{Cr} 200		346	84	498		273	39	41.2	5.9	35.3
J.O. (20 g NaCl in daily diet)	Control	C _{In} 213		753	87	711	6.53	288	75	41.4	10.8	31.1
	Aldo	C _{In} 211		312	117	322	6.10	278	30	36.8	4.0	32.8
M.U. (low NaCl diet)	Control	C _{In} 101		6.5	70	3.4		267	54	10.1	2.1	8.0
	Aldo	C _{PAH} 703		5	65	3.8		258	44	10.1	1.7	8.4

* Plotted from control periods at peak of water diuresis and from an average of two or three consecutive experimental periods taken at the observed peak effect of aldosterone on solute excretion. The corresponding electrolyte and hemodynamic values for these selected periods are given.

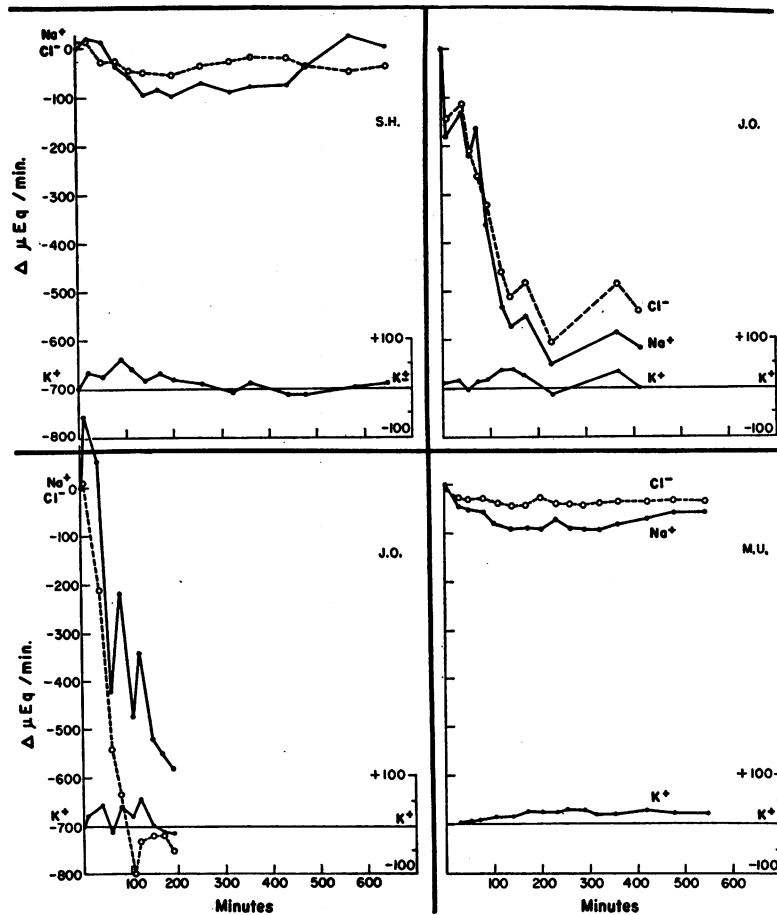


FIG. 2. EFFECT OF ALDOSTERONE ON SODIUM, POTASSIUM AND CHLORIDE EXCRETION PLOTTED AGAINST TIME IN FOUR DIFFERENT STUDIES. On the ordinates the net changes from the control values are plotted for each collection period. The increased potassium excretion is often out of phase with the reduction in sodium chloride excretion. Also the increase in potassium excretion is of considerably lesser magnitude than the reduction in sodium chloride excretion (see text).

plete results of another experiment are depicted graphically.

Effect on renal hemodynamics. Aldosterone administration produced no significant changes in either glomerular filtration rate or renal plasma flow (Tables I and II). The subjects varied considerably in their control glomerular filtration rate values from 102 ml per minute in M.U. to 213 ml per minute in J.O.; a similar variation was noted in the renal plasma flow. Because no consistent alteration was observed in a given patient in these values after injection of the hormone, the marked changes in solute and electrolyte excretion to be described were not attributable to alterations in

renal hemodynamics and therefore appeared to be due to the action of aldosterone on the renal tubules.

Effect on sodium and chloride excretion. Following aldosterone administration there was a delay of from 20 to 60 minutes before a significant reduction in sodium chloride excretion developed. During the first 20 to 60 minutes of aldosterone administration variable effects were observed, and in two of the seven studies a transient increase in sodium chloride excretion actually occurred in this early period (Figure 2, Tables I and II). Then, sodium chloride excretion was sharply reduced. The reduction reached a maximum 2 to 4 hours

after the aldosterone administration was begun. The depressed sodium chloride excretion did not return toward the control values until 6 to 8 hours after completion of aldosterone administration.

The magnitude of the sodium retention (i.e., $\Delta U_{Na}V$ from the control level) was the greatest in Subject J.O., who had the highest filtered load of sodium, and was least in Subject M.U. when he was sodium-depleted. Presumably, in this latter instance a maximal endogenous aldosterone effect was present (19, 20), and no further reduction in the $U_{Na}V$ could be produced by aldosterone administration. In the other six studies the rate of sodium excretion was reduced by from 40 to 86.5 per cent of the control values, and the absolute rate of excretion was reduced by from 59 to 441 μEq per minute in these six studies.

A parallel but, in general, lesser reduction in chloride excretion was observed. In the first six of the seven experiments (Tables I and II), chloride excretion was reduced by from 21 to 66 per cent of the control values and the decrements in rate of chloride excretion ranged from 14 to 657 μEq per minute in these six experiments. In one experiment (J.O. on 20 g NaCl intake), the fall in chloride excretion after aldosterone actually exceeded the fall in sodium output by a considerable degree. The reason for this single observation remains obscure.

That the changes observed in sodium and chloride excretion were due to aldosterone and not to prolonged water diuresis is evident from data obtained in two control studies. Water diuresis

was maintained for about 6 hours in two recumbent normal subjects. No significant changes in sodium, potassium or chloride excretion were observed during this period. In Subject O.G., whose protocol is presented in Table III, a stable water diuresis was established. Osmolar clearance fell slightly in the first 2 hours with stabilization at 2.7 ml per minute while urine volume and free water clearance (C_{H_2O}) remained relatively unchanged. In a second normal subject, E.S., a similar course of results prevailed with an average urine flow of 17.6 ml per minute in the first 190 minutes and 16.0 ml per minute in the ensuing 160 minutes. Osmolar clearance fell slightly from an average of 2.8 to 2.5 ml per minute during the same periods with a concomitant decline of free water clearance from 14.8 to 13.5 ml per minute. Average rates of electrolyte excretion in the first 190 minutes were: Na^+ , 324; K^+ , 106; and Cl^- , 424 μEq per minute; in the latter 160 minutes: Na^+ , 411; K^+ , 70; and Cl^- , 355 μEq per minute. These control studies are in agreement with the previous work of other investigators (21-23). Altogether, these results appear to exclude the possibility that the observed alterations in electrolyte excretion after aldosterone were simply a consequence of prolonged water diuresis.

Effect on potassium excretion and on urinary pH. In every experiment but one (M.U., salt-depleted) potassium excretion was at least transiently increased. The increased potassium excretion often preceded the sodium chloride retention

TABLE III
Detailed protocol of a typical control experiment *

Time	V	U _{osm}	C _{osm}	C _{H₂O}	U _{Na} V	U _{Cl} C	U _K V	Plasma			
								Osm	Na	K	Cl
min	ml/min	$\mu\text{Osm/ml}$	ml/min	ml/min	$\mu\text{Eq/min}$	$\mu\text{Eq/min}$	$\mu\text{Eq/min}$	$\mu\text{Osm/ml}$	$\mu\text{Eq/ml}$	$\mu\text{Eq/ml}$	$\mu\text{Eq/ml}$
0	1,500 ml H ₂ O p.o., 30 minutes before start of infusion to recumbent subject. 5% Dextrose and water infusion at 18 ml/min.										
+23 to 67	17.4	47	2.9	14.5	299	269	29	287	146	4.5	103
+67 to 105	18.2	45	3.4	14.8	184	212	33				
+105 to 149	17.1	42	2.5	14.6	189	159	31				
+149 to 209	18.2	42	2.7	15.5	212	175	25				
+209 to 231	17.0	43	2.6	14.4	192	169	26				
+231 to 252	17.2	43	2.7	14.5	211	208	24	275		3.9	108
+252 to 280	17.1	44	2.7	14.4	212	187	23				
+280 to 317	17.1	43	2.7	14.4	204	186	25				
+317 to 340	17.3	40	2.6	14.7	223	201	29				
+340 to +360	14.8	45	2.5	12.3	170	154	34	270	140	4.0	109
	Infusion completed.										

* Subject O.G., 71 kg white male on normal NaCl (approx. 6.0 g/day) intake.

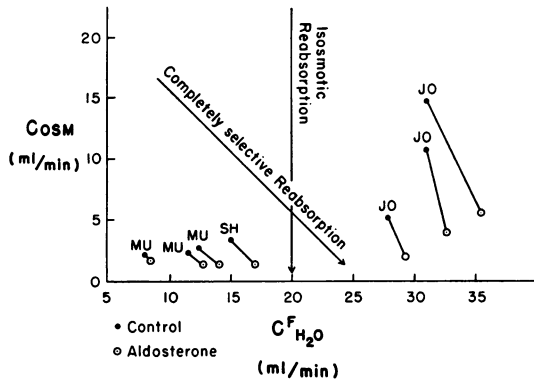


FIG. 3. EFFECT OF INTRAVENOUS ALDOSTERONE ON THE RELATION OF OSMOLAR TO FREE WATER CLEARANCE DURING A MAINTAINED WATER DIURESIS. Plotted from control periods taken at the height of water diuresis and from an average of two or three experimental periods at the peak of aldosterone effect. After aldosterone the decrement in osmolar clearance approaches or is equal to the increment in free water clearance in most of the studies. The rise in free water clearance occurs in the face of a falling osmolar clearance. The findings suggest that aldosterone abstracts sodium chloride from the urine without water.

and persisted during the periods of maximal sodium retention in only four of the seven experiments (Tables I and II; Figures 1 and 2).

The magnitude of the increased potassium excretion produced by aldosterone (ΔU_{KV}) was small, ranging from +12 to +40 μEq per minute or from +17 to +30 per cent of the control values. The increments in K^+ excretion were of similar degree in all studies and were of considerably lesser magnitude than the decrements observed in sodium chloride excretion.

The urinary pH was observed to fall following aldosterone excretion (Tables I and II). The average observed fall was 0.38 pH units at the peak of the action of the hormone on total solute excretion.

Effect on urine flow, total solute clearance and free water excretion. In all studies aldosterone was administered only after the peak of water diuresis had been achieved. The control rate of urine flow varied considerably in different subjects from 10 to 45 ml per minute. These individual variations in urine flow seemed to be related to the variations in filtered load of solute (24). After aldosterone administration, the urine flow either did not change or showed a slight decrease, such

as that which occurs in prolonged water diuresis. Therefore, the effects of aldosterone were observed during the descending limb of water diuresis.

The changes in total solute excretion after aldosterone paralleled the changes in sodium excretion both in magnitude and in phase. Thus, after an initial delay of from 20 to 60 minutes a progressive and marked reduction in urinary osmolarity ensued reaching a nadir 2 to 4 hours after the aldosterone administration. Urinary osmolarity fell to levels well below that which would be expected from water diuresis alone (21–23) (20 μOsm per ml). Thus, aldosterone facilitated the formation of an extremely dilute urine with an increased urine/plasma osmolar gradient. The urine/plasma sodium concentration gradient increased markedly in like manner.

As was the case with sodium chloride excretion, the total solute excretion did not fall appreciably in the sodium-depleted subject. However, in the other six studies total solute concentration was reduced by from 49 to 67 per cent of control values. A similar reduction in the total solute clearance (C_{osm}) was thus observed.

Since the urine flow did not change appreciably while the osmolar clearance decreased markedly, an increase in free water clearance was produced by aldosterone. In the first six experiments, the free water clearance was increased by from 1.1 to 4.3 ml per minute, but in the sodium-depleted subject, M.U., the observed changes were again slight. Since the urine flow was not rising, the calculated increases in free water cannot be attributed to an increasing water diuresis, and because solute excretion was falling, they cannot be the result of an increased solute load (24). Hence, these results imply the hypertonic abstraction of solute from the urine, i.e., reabsorption of solute unaccompanied by isosmotic amounts of water.

In Figure 3 the relationship between the osmolar clearance and the free water clearance before and after aldosterone for all seven experiments is plotted. It can be seen that after aldosterone the fall in solute clearance (ΔC_{osm}) is equal to, or almost equal to, the rise in free water clearance (ΔC_{H_2O}). In fact, in four studies of Subjects M.U. and S.H., 1 ml of free water was added to the urine for each milliliter of urine cleared of solute. This implies that aldosterone

caused the virtually totally selective abstraction of solute without water from the tubular urine.

Relationship of changes in sodium and chloride clearances to changes in osmolar clearance. Because in normal individuals sodium and chloride are the major osmolar constituents of urine and plasma and comprise the bulk of the filtered load, these solutes are the only ones available for tubular reabsorption in amounts sufficient to account for most of the free water generated during water diuresis (13). Therefore, one might assume that the changes in osmolar and free water clearance produced by aldosterone were due to the effects of the hormone on sodium (and chloride); and, in fact, in all experiments, changes in $U_{Na}V$ and in $U_{Cl}V$ closely paralleled changes in $U_{osm}V$. Aldosterone caused alterations in sodium and chloride excretion of such magnitude that, for the most part, alterations in C_{osm} produced by the hormone can be interpreted largely in terms of these ions.

In an effort to relate graphically the effect of aldosterone on sodium excretion to that on solute excretion (Figure 4), twice the C_{Na}^2 caused by the hormone has been plotted against the C_{osm} caused by the aldosterone for all experiments, with a resultant linear relationship. It can be seen that the changes of C_{osm} and thus of free water can be interpreted to be mainly a result of the effect of aldosterone on sodium (with equivalent anions). Hence, it can be concluded that aldosterone produced a fall in C_{osm} and a rise in C_{H_2O} by the abstraction of salt from a distal portion of the nephron.

Effect on urea excretion. In all experiments, the urea clearance declined gradually with no acute change observed following aldosterone administration. These data are not given in the tables.

DISCUSSION

A number of the observations made in the present study appear to confirm and extend the

² For a ΔC_{osm} of 1 ml, $1 \times P_{osm}$ (approximately 280 μOsm) was abstracted from tubular lumen. For a ΔC_{Na} of 1 ml then, $1 \times P_{Na}$ (approximately 140 μEq) of Na^+ was abstracted. Each microequivalent is an osmotically active particle. In abstraction of Na^+ an equivalent number of anions, also osmotically active particles, was removed. Hence, to relate ΔC_{Na} to ΔC_{osm} , one must multiply $\Delta C_{Na} \times 2$.

findings of other investigators. Thus, the delayed onset of action (3, 7, 25–29), the lack of effect on renal hemodynamics (2, 28, 30), the sodium and chloride retention, and the kaliuresis of aldosterone (1–13) have all been described under a variety of experimental and clinical conditions.

In the present study a latent period of about 20 to 60 minutes was observed before there was any demonstrable effect of the hormone on sodium excretion. The peak effect occurred in 2 to 4 hours, and the action lasted for as long as 6 to 8 hours after administration. In previous studies of man, other investigators have also noted a similar latent period and a similar duration of activity (3, 7, 25). Moreover, Barger, Berlin and Tulenko (26) and Ganong, Mulrow and Hollinger (31, 32), utilizing renal artery infusions, and Crabbé (27), utilizing an isolated toad bladder, have also noted the delayed onset of action of the hormone.

Mineralocorticoids such as desoxycorticosterone and aldosterone, in short-term studies, do not appear to alter renal hemodynamic function either in experimental animals (28–33) or in man (34–36). In the present study aldosterone did not produce significant changes in the renal plasma flow or in the glomerular filtration rate. There-

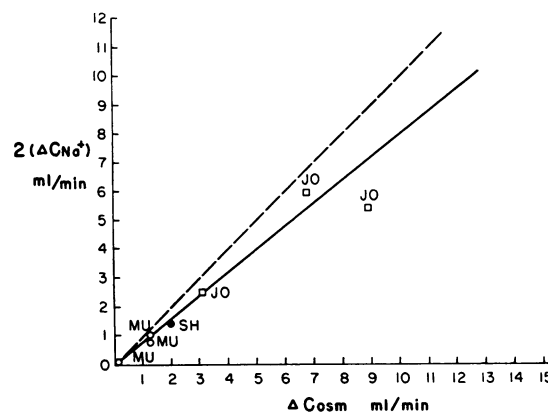


FIG. 4. RELATIONSHIP BETWEEN THE CHANGE IN OSMOLAR CLEARANCE AND TWO TIMES THE CHANGE IN SODIUM CLEARANCE PRODUCED BY ALDOSTERONE. TWO TIMES THE DECREMENT IN SODIUM CLEARANCE AFTER ALDOSTERONE ADMINISTRATION IS PLOTTED AGAINST THE CORRESPONDING DECREMENT IN OSMOLAR CLEARANCE PRODUCED BY THE HORMONE. THE PLOT ILLUSTRATES THAT THE OBSERVED CHANGES IN OSMOLAR CLEARANCE PRODUCED BY THE HORMONE ARE LARGELY ACCOUNTED FOR BY A SIMILAR CHANGE IN SODIUM REABSORPTION WITH ATTENDANT ANION.

fore, it would appear that the observed effects on electrolyte and water excretion are the result of induced alterations in the activity of tubular transport systems.

The intravenous administration of aldosterone caused increased tubular reabsorption of sodium chloride and a kaliuresis. The increased potassium excretion often began prior to salt retention, was relatively small in degree, and at times had ceased before the sodium retention had reached its peak. Similar effects of aldosterone have been described both during acute administration (2, 7, 25, 26, 31–33) and in more prolonged balance studies (1, 3–6, 37).

In the present study aldosterone usually caused sodium retention in excess of chloride, confirming the results of August and Nelson (7), who administered aldosterone intravenously with isotonic saline infusions. It thus appears that aldosterone acted to augment the active renal tubular reabsorption of sodium ion with chloride. Precedent for the stimulation of active sodium transport by aldosterone has been found *in vitro* by Crabbé (27), using an isolated toad bladder.

According to present concepts (38), filtered potassium is completely reabsorbed before the potassium destined for excretion is secreted into the tubular urine by a distal K^+ for Na^+ ion exchange process. However, while the kaliuresis observed in these experiments may have resulted from an acceleration of this ion exchange mechanism, considerable evidence indicates that the predominant effect of aldosterone—i.e., to cause sodium and chloride reabsorption—occurred independently of, and at a different locus in the distal nephron from the K^+ for Na^+ ion exchange process. Thus, the kaliuresis in general was not temporally related to the sodium retention, the magnitude of the kaliuresis was far less than the sodium retention, and the degree of kaliuresis in each subject was not related to the corresponding degree of sodium retention. Ion exchange, Na^+ for K^+ , does not explain the significant chloride retention which occurred concomitant with sodium reabsorption. Furthermore, ion exchange does not explain the reduced osmolarity of the urine after administration of the hormone, since the observed decrements in $NaCl$ excretion were, in fact, accompanied by comparable reductions in total solute excretion.

The present study demonstrates that aldosterone

can cause the abstraction of sodium chloride without water from the tubular urine, a finding which has not been reported heretofore.³ During maintained water diuresis aldosterone caused the removal of sodium chloride from the urine, producing a fall in osmolar clearance while urine flow was maintained; this resulted in a concomitant rise in free water clearance. For Subjects S.H. and M.U., the relationships between solute abstraction and free water formation were such (Figure 3) as to suggest that salt was abstracted virtually *without* water. However, in Subject J.O. the increment in free water clearance was less than the decrement in osmolar clearance indicating that, in this subject, in addition to selective sodium chloride reabsorption, some additional isosmotic reabsorption may also have been induced.

Previous studies have indicated (24, 39, 40) that, during water diuresis, there is a direct relationship between solute excretion and free water clearance, a rise in C_{osm} resulting in a rise in C_{H_2O} . Therefore, the rise in free water clearance noted after aldosterone may have more significance because it occurred in the face of a falling solute excretion. Further, because the hormone was administered only after a peak of water diuresis was achieved, when urine flow was either stable or declining, the increment in free water excretion after aldosterone administration cannot be simply the result of an increasing water diuresis.

Because aldosterone facilitates net abstraction of sodium chloride without water from the urine, it thus appears to act in the nephron at a locus distal to the site of isosmotic reabsorption. The concept that free water is formed in the more distal tubular segments by selective reabsorption of solute without water is well supported by a number of studies (14–17). Micropuncture studies have shown that in the proximal tubule, sodium reabsorption is isosmotic (14–16), while fluid from the early distal tubule has been found to be hypotonic regardless of whether the final urine is hypo- or hyperosmotic (16). Vander and co-workers, using a stop-flow technique (41), have reported that in adrenalectomized dogs, aldosterone increased the maximal concentration gra-

³ Dingman and associates measured the osmolar clearance during infusion of aldosterone. However, water diuresis was not maintained in these studies (2).

dient for sodium which could be developed between the plasma and distal tubular urine.

Because the hormone caused a distal abstraction of salt without water from the urine, an increased plasma/urine sodium concentration gradient was formed and the urine became more dilute. The results thus suggest that aldosterone is concerned with the production of a hypotonic urine. Inferential support for this role of aldosterone in urinary dilution may be derived from previous studies of electrolyte and water metabolism in adrenalectomized dogs (29, 30, 42, 43) and in patients with adrenal or pituitary insufficiency (35, 44, 45). In this group a characteristic picture is seen with low glomerular filtration, increased loss of sodium chloride (43), and a deficient ability to excrete a water load (47). Mineralocorticoid (46) alone, while promoting salt retention, does not repair the defect in water excretion. Cortisol (20, 30, 44, 46) increases the filtration rate, increases filtered sodium load, and allows more salt to be reabsorbed from the distal tubule with the production of free water and the excretion of a more dilute urine. However, this process is not very efficient, and although the ability to excrete water is improved, this occurs at the expense of substantial urinary wastage of sodium chloride. With cortisol plus a mineralocorticoid (35, 45), solute (i.e., NaCl) can be more efficiently removed from the distal tubule with both the conservation of sodium and the simultaneous production of a potentially more hypotonic urine for excretion. A similar function for the endogenous adrenal mineralocorticoid hormone, aldosterone, is implied by these data.

SUMMARY

Aldosterone (2 mg *d,l*-monoacetate) was given intravenously during a maintained water diuresis to normal subjects. No significant changes in glomerular filtration rate or in renal plasma flow were observed.

After a latent period of from 20 to 60 minutes, during which natriuresis actually occurred in two of the seven studies, the hormone produced a marked reduction in sodium with a lesser reduction in chloride excretion. The peak of this effect occurred in 2 to 4 hours.

Aldosterone also increased potassium excretion,

but this effect was often temporally dissociated from the major action of the hormone, which was to cause sodium and chloride retention.

After aldosterone administration urine flow either did not change or declined slightly; the osmolar clearance was reduced, and hence the free water clearance was increased. In some of the studies, the decrement in osmolar clearance approached or was equal to the increment in free water clearance produced by the hormone.

The results suggest that, under circumstances of water diuresis, aldosterone can promote net abstraction of sodium chloride from the urine, virtually without water, in a distal portion of the renal tubule.

The action of aldosterone results in the creation of an increased plasma/urine sodium concentration gradient and the formation of a more hypotonic urine. It is therefore suggested that the hormone plays a role in urinary dilution.

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