ELECTROLYTE EXCRETION AFTER SINGLE DOSES OF ACTH, CORTISONE,[1] DESOXYCORTICOSTERONE GLUCOSIDE,[2] AND MOTIONLESS STANDING[3]

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There are marked hourly variations in the urinary output of sodium, chloride, and potassium in normal subjects. Some of these are clearly related to intake and others are produced by major physiologic adaptations, as changing from the supine to the erect position. However, considerable variations occur from day to day and hour to hour in the fasting supine subject. The purpose of this paper is to report the variations in excretion of Na, Cl, and K in normal subjects at rest and during motionless standing and compare them with the changes produced by cortisone and desoxycorticosterone glucoside (DCG), and after adrenal stimulation by corticotropin (ACTH).

METHODS

Sodium and potassium in urine were measured by the flame photometer (1). Urinary chloride was measured by the silver iodate method (2).

Normal healthy college students were used. For three days before the experiments, the subjects were on a low-sodium diet (less than 0.5 Gm. NaCl) and were given 3 Gm. of NaCl orally every three hours. This was a daily intake of 24.5 Gm. NaCl or 422 mEq. We hoped that this high intake of NaCl would inhibit the mechanism normally causing retention of NaCl and thus allow ACTH, cortisone and DCG to have maximum action on salt excretion.

Except for water, ad lib., and 3 Gm. of NaCl every three hours, subjects were fasted for 12 hours before the experiment. In most instances, they slept in the laboratory on the night before the experiment. From 6:00 a.m. to the end of the experiment, 200 cc. of 0.5 per cent NaCl were given orally every hour and the subjects voided every hour. With the exception of the tilting experiments, the subjects remained supine throughout the period of observation. These experiments were designed to measure the effect of ACTH, cortisone, DCG and tilting on the excretion of Na, Cl, and K. The excretion rates during the first and second hours were compared with the excretion rates for the first and second hours of the control group to be certain that comparable factors were acting during all sets of experiments. Two hours after the experiment started, ACTH, DCG and cortisone were given. In determining whether significant changes had occurred after the use of drugs, comparable hours were compared with those from the control series.

RESULTS

Fasted subjects in bed without medication. Twelve experiments were run on five subjects. The hourly excretion (not recorded here) of Na, K, and Cl from 6:00 a.m. to 12:00 noon varied up and down from day to day and hour to hour in both the same and different subjects. There was no detectable correlation between the initial hourly excretion rate and the ratios Na/Cl, K/Cl, and K/Na. Over the six hours of the experiment, in spite of wide hourly variations, the quantities of Na, K, and Cl excreted progressively increased. The Na/Cl ratio showed little change. The K/Na and K/Cl ratios rose slightly in the first four hours as K excretion increased and then fell back toward the initial values as Na and Cl excretion continued to rise (data not recorded).

Intravenous ACTH. Seven experiments were run on four subjects. ACTH (Wilson) was given intravenously in three minutes in doses of 20 units at 8:00 a.m. In the first two hours before ACTH, Na excretion was somewhat less than in the fasted group ($p < .05$). The excretion of K, Cl, and Na/Cl, K/Cl, and K/Na ratios were similar to the fasted group. In the fifth and sixth hours (three to four hours after ACTH), the excretion of K and Cl had increased. The Na excretion was less than in the control group but this cannot be interpreted as representing ACTH effect, for the fasting Na excretion of this group

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[2] This drug was furnished by Dr. W. E. Wanger of the Ciba Pharmaceutical Products, Summit, New Jersey.

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was also lower than the control series. The calculated difference in means was not significant ($p > .05$). The K excretion was markedly greater than in the fasting group; the Cl excretion was the same. As compared with the fasted group there was a significant decrease in Na/Cl and significant rises in the K/Cl and K/Na ratios.

Oral cortisone. Four experiments were done on two subjects. One hundred milligrams of cortisone was given orally at 8:00 a.m. Compared to the fasted group, there was no significant difference in the excretion of Na, K, Cl, or in the Na/Cl, K/Cl, and K/Na ratios before cortisone was given. At the fifth and sixth hours (third and fourth hours after cortisone) there was not a significant rise in Na excretion, but Cl and K excretion were increased. As compared to the fasted group there was a significant increase in the excretion of K, but no difference in the excretion of Na and Cl. However, in the third and fourth hours after cortisone the Na/Cl ratio showed a significant fall and the K/Cl and K/Na ratios showed a significant rise.

Intravenous desoxycorticosterone glucoside. Five experiments were done on two subjects. They received 50 mg. of DCG intravenously at 8:00 a.m. Comparison of the control first and second hours with the first and second hours before DCG was given showed no significant difference in excretion of Na, K, and Cl and no difference in the Na/Cl, K/Cl, and K/Na ratios. In the fifth and sixth hours of observation (third and fourth hours after DCG), the excretion of K had risen but there was no significant rise in excretion of Na and Cl. In comparison to the fasted group, DCG caused a retention of Na and Cl. The K excretion was no greater than in the control group. There was a significant fall in Na/Cl ratio and a significant rise in the K/Cl and K/Na ratios.

Tilt. Twelve experiments were done on five subjects. Comparison of excretion of Na, K, and Cl and Na/Cl, K/Cl, and K/Na ratios in the first two hours with the fasted group showed no significant differences. As compared to the unpublished three to four hour control period, in the first and second hours after head up tilt at an angle of 45 degrees above the horizontal, there was a striking decrease in excretion of Na and Cl. K excretion was not reduced in absolute amounts but did not show the rise seen in the subjects remaining flat. Tilting caused a fall in Na/Cl ratio and a rise in K/Cl and K/Na ratios.

DISCUSSION

These data show that in the doses used, ACTH, cortisone and DCG have a similar effect on the patterns of excretion of Na, Cl, and K. No definite changes are present until after two hours.

TABLE I

Comparison of excretion of Na, K, Cl in mEq. and Na/Cl, K/Cl, K/Na ratios *

	Hours†	Na SE	p*‡	K SE	p*	Cl SE	p*	Na/Cl SE	p*	K/Cl SE	p*	K/Na SE	p*
Control	1–2	15.3±1.45 (10)		3.1±0.43 (7)		16.0±1.52 (10)		0.858±0.053 (7)		0.214±0.025 (7)		0.219±0.018 (7)	
	5–6	22.8±1.32		5.4±0.42		25.8±1.38		0.902±0.035		0.213±0.017		0.256±0.013	
	p#‡	<.01		<.01		<.01		>.05		>.05		>.05	
ACTH	1–2	11.1±1.32 (7)	<.05	2.3±0.44 (7)	>.05	12.6±1.56 (7)	>.05	0.887±0.022 (7)	>.05	0.230±0.025 (7)	>.05	0.260±0.028 (7)	>.05
	5–6	15.0±1.74	<.01	9.3±0.41	<.01	22.7±1.95	>.05	0.696±0.024	<.01	0.424±0.038	<.01	0.723±0.029	<.01
	p#	>.05		<.01		<.01		<.01		<.01		<.01	
Cortisone	1–2	14.6±2.2 (4)	>.05	3.4±0.41 (4)	>.05	14.8±2.2 (4)	>.05	0.974±0.024 (4)	>.05	0.176±0.022 (4)	>.05	0.202±0.025 (4)	>.05
	5–6	19.8±1.16	>.05	7.4±0.51	<.01	25.8±1.2	>.05	0.771±0.041	<.05	0.287±0.022	<.05	0.391±0.048	<.05
	p#	>.05		<.01		<.01		<.01		<.01		<.01	
DCG	1–2	12.8±1.61 (5)	>.05	2.6±0.40 (5)	>.05	13.7±2.26 (5)	>.05	0.923±0.030 (5)	>.05	0.199±0.016 (5)	>.05	0.220±0.022 (5)	>.05
	5–6	12.9±2.24	<.01	6.6±0.62	>.05	18.7±1.42	<.01	0.664±0.046	<.01	0.365±0.040	<.01	0.618±0.115	<.01
	p#	>.05		<.01		>.05		<.05		<.01		<.01	
Tilt	1–2	14.5±1.25 (12)	>.05	2.6±0.38 (6)	>.05	18.7±1.67 (6)	>.05	0.813±0.039 (12)	>.05	0.185±0.010 (12)	>.05	0.202±0.045 (12)	>.05
	3–4	6.5±0.93	<.01	2.4±0.25	<.01	9.3±1.03	<.01	0.693±0.025	<.01	0.295±0.035	<.01	0.489±0.033	<.01
	p#	<.01		>.05		<.01		<.02		<.01		<.01	

* Numbers in parentheses indicate the number of experiments.
† "1–2" means excretion during first and second hours; "5–6" means excretion during fifth and sixth hours.
‡ p* as compared to the corresponding period in the control. p# as compared to the first two hours of experiment.

The pattern of changes consists of a relative decrease in the excretion of Na as compared to Cl and an increase in the excretion of K as compared to the excretion of Na and Cl. In the data reported here the changes in Na/Cl, K/Cl, and K/Na ratios proved a more easily measurable index of the activity of the drugs tested than did the measurement of the amount of each electrolyte excreted. In the doses used, only DCG caused demonstrable retention of Na and Cl. Both ACTH and cortisone caused an increased excretion of K. In observations on rats the K/Na has been found to be a more delicate indication of desoxycorticosterone activity than the absolute of Na and K excretion (3).

Other authors giving ACTH intramuscularly have reported that an increased excretion of Na, Cl, and K occurs after a single dose (4, 5). These authors studied the excretion of electrolytes in the morning after omitting breakfast. No data are given to demonstrate that the increased rates of electrolyte excretion are actually caused by ACTH and not due to combination of increased K excretion expected from fasting (6) and the increased NaCl excretion which may occur spontaneously in the morning hours (7).

The hour-to-hour variations in excretion of Na and Cl on the same and different days do not appear to be solely controlled by increases and decreases in hormonal activity of a type similar in action to cortisone and DCG or adrenal stimulation by ACTH. If these variations were the result of such changes in hormonal activity, one might expect to find a correlation between the amounts excreted and the pattern of excretion of Na, K, and Cl. These are not found.

Tilting to the head-up position causes a striking decrease in the excretion of Na and Cl. Both in time and magnitude the effect is dissimilar to that seen after ACTH, cortisone, and DCG. K excretion is unchanged and this results in a rise in K/Cl, K/Na ratios. The Na/Cl ratio falls, indicating a greater retention of Na than Cl.

Although tilting produces the same pattern of changes in ratios as did the drugs tested, these observations do not support the thesis that the absolute retention of Na, Cl, and K on tilting to the head-up position is caused primarily by release of a hormone having the activity of cortisone or DCG or adrenal stimulation by ACTH. The changes in the ratios leave unanswered the possibility that an increase in adrenal activity produced by ACTH might be responsible for the relatively greater excretion of Cl and K in comparison to Na. These data do not bear on the question of the production of other salt-retaining steroids by the adrenals. It has recently been shown that l-epinephrine and l-norepinephrine cause retention of Na and K (8, 9). Increased production of these compounds during motionless standing may occur.

SUMMARY

1. In normal fasted subjects on a constant intake of NaCl for three days, there are striking variations in the excretion of NaCl between 6:00 a.m. and 11:00 a.m. In subjects receiving 200 cc. of 0.5 per cent NaCl solution from 6:00 a.m. to 11:00 a.m., there is a rise in K excretion and an irregular but definite increase in the excretion of Na and Cl.

2. Single doses of ACTH (20 units i.v.), cortisone (100 mg. orally), and desoxycorticosterone glucoside (50 mg. i.v.) cause a change in electrolyte excretion detectable in the third and fourth hours after their administration. The Na/Cl ratio falls and K/Cl and K/Na ratios rise. Under the condition of these experiments only DCG caused a demonstrable retention of Na and Cl. ACTH and cortisone increased the excretion of K. None of these drugs caused an increased excretion of Na or Cl.

Head-up tilting to an angle of 45 degrees produced a fall in electrolyte excretion which began in the first hour and was of an order of magnitude not seen with the drugs used. It appears unlikely that stimulation of the adrenal by ACTH or the production of cortisone or DCG is important in the striking salt retention produced by motionless standing.

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