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EFFECT OF STEROIDS ON WATER DIURESIS AND VASOPRESSIN SENSITIVITY *

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The ability of glucocorticoids to reverse the abnormal diuretic response to water in adrenal insufficiency (1–5) and to increase water diuresis in normal subjects (6, 7) is well known. Although glucocorticoids appear to be specific in this regard, the possibility that other steroids may have a pharmacologic effect on water diuresis in normal man has not been investigated systematically. The present study was therefore undertaken to compare the effects of large doses of cortisol, progesterone, estrogen and aldosterone on the maximal rate of free water clearance during water diuresis in normal man. The effects of low sodium diet and an aldosterone antagonist also were examined. It was found that only cortisol appeared to have a specific effect on this rate. Variations in maximal water diuresis also were encountered in control studies and after treatment other than cortisol, but these appeared to be related to changes in total solute excretion.

It has been suggested that glucocorticoids may antagonize the action of antidiuretic hormone (1, 6, 8). To test this possibility, the effect of a constant infusion of a submaximal dose of exogenous vasopressin on water diuresis was examined before and after treatment with cortisol and other steroids. Variations in the response to vasopressin were encountered which were related to variations in the initial maximal rate of water diuresis in control studies. None of the agents tested, including cortisol, appeared to alter this relationship.

METHODS

Five healthy, paid volunteer medical students served as subjects. The experiments were performed in the postabsorptive state, but at different times of day. After an initial oral water load of 20 ml per kg of body weight, the subject maintained water diuresis by drinking an amount of water equal to the amount voided during the last urine collection period. Urine collections were obtained by voluntary voiding at 15-minute intervals. An infusion of 5 per cent dextrose in water was maintained at a constant rate of 0.6 or 1.2 ml per minute throughout the experiment. Blood samples for determination of total solute, electrolyte and creatinine concentration were obtained at the beginning and the end of the infusion. In order to minimize antidiuretic stimuli, no injection or venipuncture was performed during the experiment except for 3 experiments in Subject L.B., in which inulin clearance was measured. After a steady rate of water diuresis had been established for at least 3 periods, the infusion was changed to one containing vasopressin in an amount to provide 4, 8, 12 or 16 mU per hour. A freshly opened ampule of commercial vasopressin (Pitressin; Parke, Davis & Co.) was used for each experiment. One lot (S216F) was used for 4 subjects. The lot used in Subject L.B. (Y108HA) had less antidiuretic potency when the two lots were compared in the same experiment. In most experiments, the response to a single rate of vasopressin administration was observed. In selected experiments, two different rates were used. Each rate was continued for 90 to 120 minutes, until the urine flow was again steady. After vasopressin was discontinued, the return to a new steady state of maximal water diuresis was observed. This usually required 75 to 90 minutes. The data from such experiments are presented as the mean values for 2 to 4 consecutive periods in which urine flow did not vary by more than 10 per cent during maximal water diuresis, or by more than 0.5 ml per minute during vasopressin infusion.

In addition to 3 or 4 control experiments in each subject, the experiments were repeated after the following forms of treatment.

1. Cortisol. Three subjects took 40 mg of cortisol orally every 6 hours for 4 days.

2. Progesterone. Two subjects received intramuscular injections of 100 mg of progesterone in oil every 12 hours for 4 days.

3. Estrogen. Two subjects took 0.1 mg of ethinyl estradiol orally every 6 hours for 7 days.

4. Aldosterone. Three subjects received intramuscular injections of 0.3 mg of *dl*-aldosterone monoacetate every 6 hours for 3 days. A fourth subject (R.B.) was studied after 1 day of aldosterone administration.

5. Low salt diet. Three subjects ingested a 200 mg sodium diet for 3 to 5 days prior to study.

6. Spironolactone. At the completion of the experiment on a low sodium diet, these subjects took 200 mg of spironolactone, an aldosterone antagonist, orally every 6 hours for 2 days while remaining on a low sodium intake. A fourth subject (A.G.) was studied after receiving spironolactone for 4 days while on an unrestricted diet.

Chemical methods and calculations

Methods for determination of osmolality, creatinine, sodium and potassium have been described previously from this laboratory (9). The net excess of water in the urine, or free water clearance (C_{H_2O}), was calculated as the difference between urine flow and osmolal clearance. Creatinine clearance values served as a check on the constancy of bladder emptying and as a rough measure of glomerular filtration rate. Inulin clearance (10) was measured in three experiments in Subject L.B. Antidiuresis occurred with blood sampling and at the time of injection of the inulin prime, and the experiments had to be prolonged in order to obtain data on steady state water diuresis. For this reason, inulin clearance was not measured in any other experiments. The response to vasopressin was measured as the change in free water clearance which occurred between the ini-

tial maximal water diuresis and the steady state during vasopressin infusion. This has been termed ΔC_{H_2O} (11).

RESULTS

The results are summarized in Table I.

I. Maximal water diuresis. Values for free water clearance during maximal water diuresis varied considerably. In control studies, changes in maximal C_{H_2O} could be related to variations in total solute excretion (Figure 1). This relationship was observed whether the variation in solute excretion could be related to diurnal rhythm or to a change in dietary intake. Although sodium excretion and total solute excretion often were parallel, the former showed a greater variability, and the correlation between sodium excretion and C_{H_2O} was not significant in control experiments. Data obtained after progesterone and estrogen administration showed slightly high values for sodium excretion, total solute excretion and C_{H_2O}. After intramuscular administration of aldosterone, sodium excretion was somewhat decreased compared with the mean control values, and potassium excretion was increased. However, total solute excretion and C_{H_2O} decreased only in Subject L.B. A marked decrease in sodium excretion and a de-
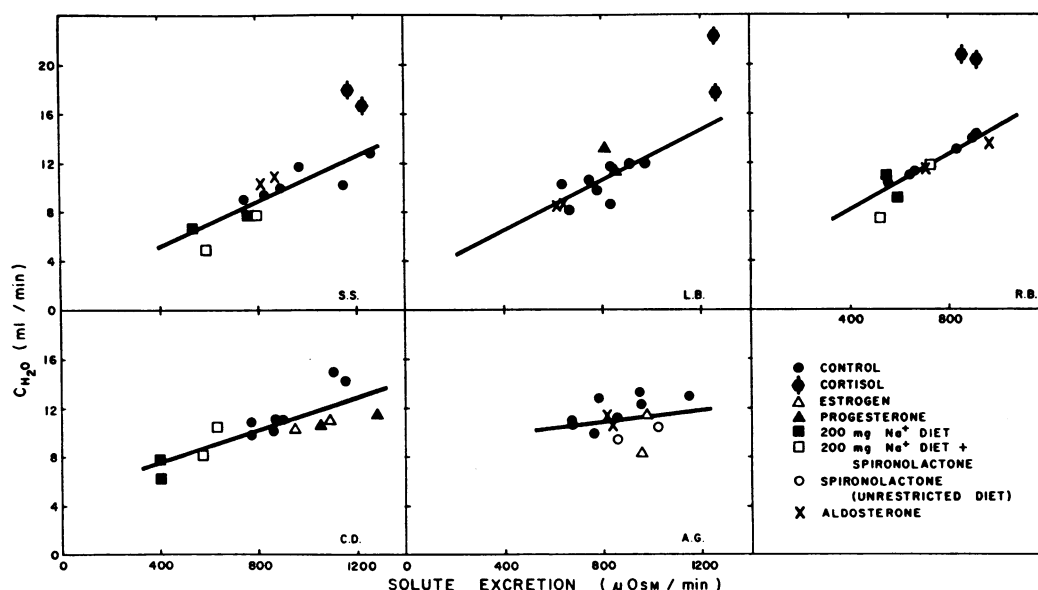
Fig. 1. MAXIMAL FREE WATER CLEARANCE (C_{H_2O}) VERSUS TOTAL SOLUTE EXCRETION. Data are shown for the subjects individually before and after the administration of cortisol, estrogen, progesterone, aldosterone, a low sodium diet and an aldosterone antagonist. The solid lines represent the regression line calculated by the method of least squares for all data for each subject exclusive of values obtained after cortisol administration.

TABLE I

Water diuresis and vasopressin response in normal young men.   Control studies and effect of cortisol (Cort), progesterone (Prog), estrogen (Estr), aldosterone (Ald), 200 mg sodium diet (Low Na) and spironolactone on low sodium diet (Sp + low Na) or on unrestricted diet (Sp) are shown.   Time given is for the beginning of vasopressin infusion

Subject Age Surface Area	Study Date Time	Vaso-pressin mu/hr	Urine Flow ml/min	Urine Osmolality mOsm/L	Solute Excretion μOsm/min	CH₂O ml/min	Sodium Excretion μEq/min	Creatinine Clearance ml/min	ΔCH₂O ml/min
S. S. 24 1.98m²	Control 10/16/59 9:30 am	0 4 0	15.0 6.8 13.1	65 158 68	974 1071 896	11.6 3.0 9.9	126 194 130	104 99 100	 8.6
	Cort 10/23/59 9:45 am	0 4 8 0	20.5 8.5 2.8 21.8	60 98 312 53	1230 837 874 1155	16.3 5.6 -.3 17.7	240 71 120 292	146 120 140 155	 10.7 16.6
	Control 11/2/59 9:45 am	0 4 8 0	16.8 4.5 1.7 14.0	76 190 469 78	1265 849 769 1102	12.3 1.5 -1.1 10.1	189 190 234 305	123 121 119 112	 10.8 13.4
	Low Na 11/6/59 10:15 am	0 4 0	10.4 3.1 8.5	73 167 64	760 512 538	7.7 1.2 6.5	7 12 41	115 104 107	 6.5
	Sp+low Na 11/9/59 10:30 am	0 4 0	10.5 2.4 6.8	76 254 87	798 613 596	7.7 .2 4.7	110 78 70	112 103 	 7.5
	Control 2/27/60 12:45 pm	0 4 0	11.6 4.1 12.3	64 164 68	748 675 828	8.9 1.7 9.3	43 128 146	104 117 119	 7.2
	Ald 3/5/59 1:30 pm	0 4 0	14.1 4.9 13.9	58 151 62	817 744 870	11.2 2.3 10.8	76 84 158	122 113 119	 8.9
C. D. 24 2.03m²	Control 7/22/59 9:45 am	0 8 0	18.8 5.4 12.6	58 168 61	1100 895 769	14.9 2.1 9.8	120 115 160	155 142 191	 12.8
	Prog 7/29/59 10:00 am	0 8 0	16.0 4.4 14.3	79 238 73	1280 1060 1055	11.5 0.6 10.5	201 230 175	144 128 127	 10.9
	Control 10/2/59 2:30 pm	0 8 0	14.2 5.0 14.3	63 172 62	896 860 870	11.0 1.9 11.1	72 152 137	122 144 138	 9.1
	Estr 10/9/59 1:30 pm	0 8 0	14.8 5.5 13.7	73 205 69	1083 1121 944	10.9 1.4 10.3	188 282 202	138 161 145	 9.5
	Control 11/18/59 10:30 am	0 8 0	18.3 5.2 13.6	63 150 54	1147 772 738	14.1 2.3 10.8	161 99 106	102 112 123	 11.8
	Low Na 11/23/59 1:30 pm	0 8 0	7.8 0.7 9.3	52 479 44	404 356 404	6.3 -.6 7.8	9 2 12	148 152 126	 6.9
	Sp+low Na 11/25/59 10:00 am	0 8 0	12.8 3.4 10.3	50 193 56	635 652 578	10.4 0.9 8.1	41 65 40	128 132 87	 9.5
R. B. 24 1.80m²	Control 11/4/59 9:45 am	0 4 8 0	13.6 8.6 2.0 17.2	49 90 348 52	665 774 696 895	11.2 5.8 -.5 14.0	43 97 124 172	89 101 99 102	 5.4 11.7
	Cort 11/14/59 12:45 pm	0 4 8 0	23.5 14.6 6.6 23.8	39 56 121 36	916 817 802 856	20.2 11.6 3.6 20.6	91 92 112 169	105 101 78 110	 8.6 16.6
	Control 11/27/59 11:15 am	0 4 0	12.4 7.4 15.6	45 92 42	558 677 646	10.3 4.8 13.0	25 101 70	78 83 	 5.5
	Low Na 11/30/59 1:30 pm	0 4 0	11.3 4.7 13.0	54 122 42	597 572 546	9.1 2.6 10.9	4 7 8	97 95 	 6.5

Table I. (cont.)

Subject Age Surface Area	Study Date Time	Vaso- pressin mu/hr	Urine Flow ml/min	Urine Osmolality mOsm/L	Solute Excretion μOsm/min	CH_2O ml/min	Sodium Excretion μEq/min	Creatinine Clearance ml/min	ΔCH_2O ml/min
R. B. (cont.)	Sp+iow Na	0	9.2	57	525	7.3	19	99	
	12/2/59	4	4.5	117	531	2.5	35	94	4.8
	10:30 am	0	14.2	50	704	11.6	83	98	
	Control	0	15.9	52	832	12.9	77	105	
	12/19/59	4	10.2	92	950	6.8	196	100	6.1
	10:30 am	0	17.4	52	907	14.1	305	110	
	Ald	0	14.0	50	706	11.5	38	103	
	12/28/59	4	8.7	105	911	5.4	116	105	6.1
	10:30 am	0	16.9	57	965	13.4	155	102	
A. G.	Control	0	16.9	68	1150	12.9	286	146	
25	4/17/59	8	3.3	240	800	.5	162	127	12.4
1.80m²	10:45 am	0	15.6	50	782	12.8	142	172	
	Control	0	15.6	61	959	12.2	95	144	
	9/11/59	8	2.5	286	720	-.1	140	149	12.3
	10:00 am	0	14.2	61	862	11.1	164	172	
	Estr	0	14.7	66	978	11.3	126	208	
	9/20/59	8	4.1	290	1178	-.2	210	181	11.5
	10:45 am	0	11.7	82	950	8.2	178	142	
	Control	0	13.2	51	675	10.8	72	171	
	10/5/59	8	2.4	268	623	.1	116	150	10.7
	10:45 am	0	16.7	56	951	13.2	225	179	
	Sp	0	14.1	72	1021	10.4	184	148	
	10/10/59	8	3.0	316	947	-.4	200	142	10.8
	11:00 am	0	12.4	70	860	9.3	155	154	
	Control	0	12.5	62	765	9.8	68		
	11/16/59	8	1.1	551	584	-1.1	55		10.9
	2:00 pm	0	13.2	51	673	10.7	140		
	Ald	0	13.8	60	818	10.8	103		
	3/5/60	8	2.8	300	830	-.2	106		11.0
	10:30 am	0	13.6	62	842	10.6	103		
L. B.	Control	0	14.7	56	830	11.7	109	92	
26	12/31/59	8	12.4	67	830	9.4	120	115	2.3
2.00m²	1:45 pm								
	Control	0	10.5	64	666	8.1	33	95	
	1/8/60	16	1.9	281	525	.0	77	100	8.1
	1:45 pm	0	12.6	50	635	10.2	105	105	
	Prog	0	14.6	58	842	11.6	104	122	
	1/15/60	16	4.1	169	687	1.6	63	107	10.0
	1:15 pm	8	9.6	78	744	6.8	112	110	4.8
		0	16.1	50	807	13.1	161	114	
	Control	0	11.4	73	833	8.5	89	134*	
	1/22/60	16	3.4	211	694	0.9	94	120	7.6
	2:00 pm	0	13.2	56	746	10.6	80	143	
	Ald	0	10.4	59	615	8.2	38	134*	
	1/29/60	12	4.1	153	621	1.9	70	135	6.3
	2:45 pm	0	10.8	59	634	8.6	79	128	
	Control	0	15.1	60	908	11.9	75	132	
	2/5/60	12	6.9	128	880	3.7	111	110	8.2
	10:00 am	8	9.2	89	821	6.3	111	106	5.6
		0	12.6	61	778	9.8	61	126	
	Cort	0	22.4	56	1265	17.8	336	130*	
	4/9/60	16	9.9	124	1236	5.5	215	125	16.9+
	12:00 am	8	22.6	63	1418	17.6	318	132	4.8+
		0	26.8	47	1261	22.4	328	136	

*Mean inulin clearance values were 109 ml. per minute for Control experiment, 115 ml. per minute after Aldosterone and 160 ml. per minute after Cortisol.

+Water diuresis was increasing when vasopressin infusion begun, therefore, ΔCH_2O was measured from final water diuresis in this experiment.
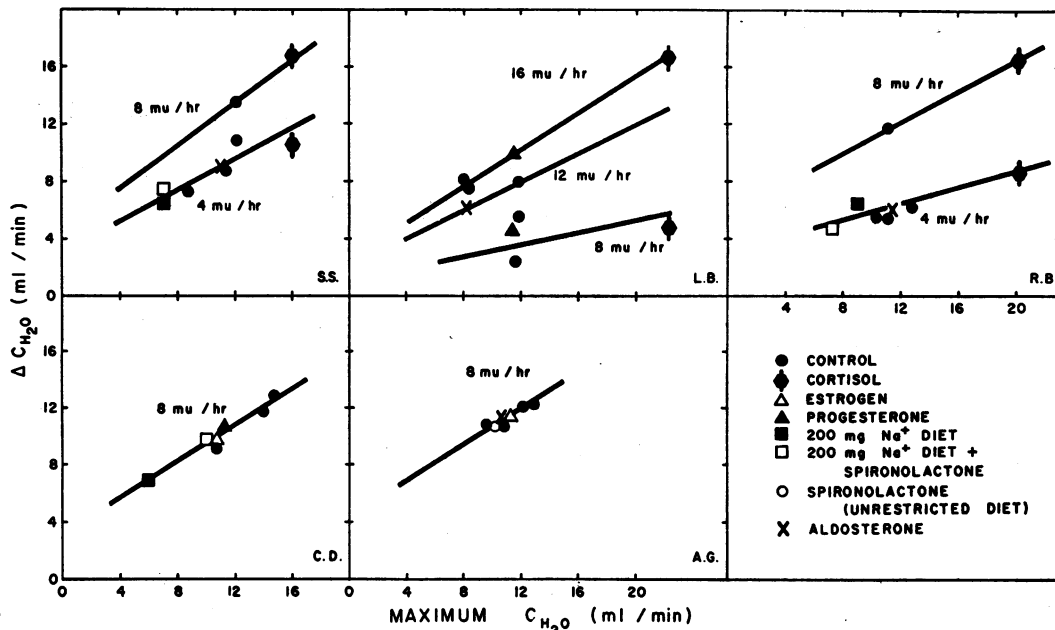
Fig. 2. Vasopressin response (ΔC_{H_2O}) versus maximal free water clearance (maximal C_{H_2O}). Data are shown for subjects individually before and after the administration of cortisol, estrogen, progesterone, aldosterone, a low sodium diet and an aldosterone antagonist. The regression lines shown were drawn visually to represent the equation $\Delta C_{H_2O} = k$ (max. $C_{H_2O} + a$). The intercept on the abscissa (value of constant a) was the same at two different dose levels in Subjects S.S., L.B. and R.B. The response to 8 mU per hour of a less potent vasopressin preparation in L.B. was less consistent.

crease in total solute excretion and C_{H_2O} was observed on a low salt diet. When spironolactone was administered to these subjects, sodium excretion increased strikingly, but this was accompanied by an increase in C_{H_2O} and total solute excretion only in Subject C.D. In all of the foregoing experiments, the relationship between total solute excretion and C_{H_2O} was similar to that observed in control studies. After cortisol administration, there was a variable increase in sodium and total solute excretion; however, C_{H_2O} increased markedly in each subject out of proportion to the change in solute excretion.

Creatinine clearance values could not be related to changes in C_{H_2O} in the present study. Subject S.S. showed a rise in creatinine clearance on cortisol. In Subject L.B., inulin clearance increased on cortisol but creatinine clearance did not. Creatinine clearance was not altered consistently by any of the other treatments studied.

II. Vasopressin sensitivity. The response to a given dose of vasopressin, in terms of its effect on free water clearance (ΔC_{H_2O}), was not constant in the same subject (Figure 2). As the value of C_{H_2O} obtained during initial maximal water diu-

resis increased, the value for ΔC_{H_2O} obtained in the steady state by the infusion of a given dose of vasopressin also increased. This relationship can be described by the equation:

$$\Delta C_{H_2O} = k \text{ (maximal } C_{H_2O} + a)$$

where k is a constant which varies with the dose of vasopressin and a is a constant amounting to 4 to 10 ml per minute in different subjects. For the few data available, the value of a appeared to be the same at different dose levels in the same subject. This relationship between ΔC_{H_2O} and maximal C_{H_2O} accounts for much of the variability encountered both in control studies and after treatment. Thus, the increase in maximal C_{H_2O} after cortisol administration is accompanied by an increase in ΔC_{H_2O}, particularly in response to the infusion of larger doses of vasopressin.

DISCUSSION

Variations in the diuretic response to a water load which cannot be attributed to changes in endogenous antidiuretic hormone production have been described previously. These have been related to glomerular filtration rate (12), solute

excretion (12, 13) and sodium excretion (13, 14). In the present study, a close relationship between maximal C_{H_2O} and total solute excretion was observed in normal subjects with diurnal, dietary and hormonally induced variations in solute excretion. It is possible that under these circumstances variations in both C_{H_2O} and total solute excretion are determined by the amount of sodium and water delivered to the distal diluting site. Subsequent variations in reabsorption and exchange of sodium in the distal tubule could account for the lack of correlation between urinary sodium and C_{H_2O}. In osmotic diuresis delivery of non-reabsorbable solute to the distal tubule can result in an increase in solute excretion without an associated increase in C_{H_2O} (14–16).

As previously noted (7), cortisol increases C_{H_2O} out of proportion to its effect on total solute excretion. This increase has been attributed to the effect of an increase in glomerular filtration rate, together with either a redistribution of solute reabsorption between proximal and distal tubules, or an alteration in tubular permeability to water (5, 7).

A few observations are available which suggest that maximal water diuresis is increased in pregnancy (17, 18). Progesterone administration has been reported to enhance the rate of water elimination in rats (19) while estrogen has no effect (6). In the present study, progesterone and estrogen had little effect on water diuresis in normal young men. Moreover, in preliminary experiments, water diuresis showed no consistent variation at different phases of the menstrual cycle in normal young women (20).

Conceivably, aldosterone could alter the relationship between C_{H_2O} and solute excretion by enhancing direct sodium reabsorption at sites where free water is made available. In the present study, such an effect could not be detected with exogenous aldosterone or when endogenous aldosterone production was increased by sodium restriction. Similarly, an aldosterone antagonist failed to decrease free water clearance. However, the variability of water diuresis in these chronic experiments may have masked slight alterations in C_{H_2O} caused by aldosterone.

It is possible that small changes in glomerular filtration rate could account for the changes in C_{H_2O} and total solute excretion observed in the present study. Creatinine clearance measurements could not detect such changes, particularly where only initial and final blood values were measured. Unfortunately, we have been unable to obtain inulin clearance measurements without interfering with maximal water diuresis in our subjects.

In the present study, ΔC_{H_2O} in response to a given dose of vasopressin was found to vary with the initial value of maximal C_{H_2O}. Hollander, Williams, Fordham and Welt (11) also noted an increase in ΔC_{H_2O} in response to the same dose of vasopressin in experiments in which solute excretion was increased and initial maximal C_{H_2O} was high. Theoretically this relationship would be expected if the action of vasopressin were to increase the permeability of the cell membrane (21), since the amount of water reabsorbed would then depend upon the mean osmotic gradient along the distal tubule during vasopressin administration. When more free water was available in the distal tubule, the amount reabsorbed in response to vasopressin was greater, but the final urine was also more dilute. Both the lower urine osmolality and the larger value of ΔC_{H_2O} would appear to be the physicochemical consequence of the change in available free water and do not indicate a specific change in the sensitivity of the renal tubules to vasopressin. On the other hand, more endogenous antidiuretic hormone secretion may be required to concentrate the urine and maintain the water economy under conditions when maximal C_{H_2O} is increased. This change in requirement would apply whether C_{H_2O} was altered by cortisol or by any other means (15).

Whatever its theroetical basis, the observed relationship between ΔC_{H_2O} and maximal C_{H_2O} can be used to assess variations in vasopressin response under experimental conditions. Previous studies on the effect of glucocorticoids on vasopressin response based on the effect of a single injection (7) indicated that the tubule was not insensitive to the action of ADH. Using the more precise technique of the present study, neither cortisol nor any of the other steroids tested altered the sensitivity of the renal tubule to vasopressin.

SUMMARY

The maximal rate of water diuresis and the response to a constant infusion of vasopressin were

studied before and after the administration of cortisol, progesterone, estrogen, aldosterone, a low sodium diet and an aldosterone antagonist in healthy young men.

Variations in free water clearance during maximal water diuresis were observed. These variations could be related to changes in total solute excretion in control experiments. This relationship was not altered by any of the treatments except cortisol administration. After cortisol administration, free water clearance increased more than would be expected from the change in solute excretion.

The decrease in free water clearance observed with the infusion of a given submaximal dose of vasopressin was directly related to the initial maximal rate of free water clearance. This relationship was unchanged by treatment, including cortisol administration.

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