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Research Article

THE EFFECT OF DESOXYCORTICOSTERONE ACETATE ON WATER AND ELECTROLYTE DISTRIBUTION [1]

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Previous evidence has indicated that in dog and man, the administration of adrenal hormones effects a temporary shift of sodium, chloride, and water in iso-osmotic proportions into the extracellular fluid (1, 2). This conclusion was based on the assumption that inulin afforded a reliable measure of the volume of the fluid phase of the extracellular compartment (3). It has been contended that after the administration of adrenal hormones a molecule like inulin might enter areas from which it was previously excluded (4). In this event, the increased volume of distribution of inulin would not reflect an expanded extracellular volume but rather a change in tissue permeability to inulin. To test the validity of the original conclusion, similar experiments were repeated in monkeys. In this protocol inulin spaces were measured before and after five days of desoxycorticosterone acetate (DCA) administration to monkeys. As in the experiments previously cited (1, 2), the animals were maintained on a low salt intake so that any expansion of the inulin space could not be attributed to retention of salt. In these experiments, however, sodium, chloride, potassium, and water content of muscle were studied in control animals and in those subjected to DCA administration. Tissue electrolyte composition was measured to determine whether the expanded inulin space would be associated with a comparable increase in sodium and chloride content of muscles. Such a correspondence would strongly favor the hypothesis that the extracellular volume had actually increased. Alternatively, it would be difficult to accept the presence of an expanded extracellular volume without a proportional increase in the salt content of muscle.

It has been demonstrated that the stimulus of severe and uncompensated acidosis evokes a rapid transfer of sodium from bone and tendon into the extracellular fluid (5, 6). Assuming that adrenal hormone administration actually does produce a transfer of sodium, chloride and water into the extracellular fluid, it was considered likely that bone and dense connective tissue might provide a source of those electrolytes. Accordingly, the electrolyte and water composition of bone and tendon as well as muscle were measured in both control and hormone treated monkeys.

MATERIALS AND METHODS

These studies were performed on unanesthetized, adult, male cynomolgus monkeys. Female animals were not used in order to avoid the possible effects of hormonal changes upon water and electrolyte metabolism. Anesthetic agents were avoided since these have been shown to exert an effect upon the distribution of body fluids (7).

Pre-treatment control values for normal body weight, volume of distribution of inulin, inulin clearance (GFR), and plasma sodium, potassium and chloride concentrations were obtained in each monkey studied. Thereafter, each animal received 10 mg. of DCA intramuscularly daily for five days. Body weight, volume of distribution of inulin and plasma electrolyte concentrations were again determined. As soon as these measurements were completed, the animals were sacrificed and tissue samples of muscle, bone and tendon were obtained. Beginning five days before the pre-treatment studies, each monkey received a diet of one orange, three bananas, and distilled water *ad libitum* daily. On analysis, this diet contained 0.13 mEq. of sodium, 31.0 mEq. of potassium and 2.5 mEq. of chloride per day. The electrolyte and water content of the tissues of the control group were determined in untreated normal monkeys of comparable weight. The control animals were maintained on the same low salt diet as the hormone treated group for a period of eight to ten days before they were sacrificed.

The volume of distribution of inulin (fluid phase of the extracellular compartment, inulin space) was determined by the post-infusion technique (8, 9) wherein the plasma inulin concentration (corrected for blank) present at the end of an equilibrating infusion is divided into the amount of inulin excreted in the urine after a steady equilibrating infusion has been discontinued. Inulin clearances were performed by standard methods previously used in this laboratory.

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TABLE I

Body weight and inulin space before and after DCA administration

Monkey number	Weight		Inulin space	
	Kg.		*ml.*	%
25	5.8	Control	955	
	5.8	DCA	1216	
		Difference	+261	27
39	5.8	Control	908	
	5.5	DCA	1280	
		Difference	+372	41
44	7.4	Control	1214	
	6.9	DCA	1512	
		Difference	+298	25
45	5.1	Control	680	
	5.0	DCA	922	
		Difference	+242	35
46	4.1	Control	552	
	4.1	DCA	784	
		Difference	+232	42

The animals were sacrificed by decapitation in order to avoid the influences of anesthetic agents, exsanguination or prolonged agonal states. Immediately thereafter, tissue samples were obtained and cleaned of as much fat and connective tissue as possible. All marrow and periosteum were removed from bone specimens so that only the cortical portion remained. The samples were placed in weighing bottles, minced and weighed immediately. The tissues were then placed in a drying oven (100° to 105° C.) for 48 hours, by which time constancy of weight was attained. Bone required a longer period of drying (five days). The total water content of the tissues was calculated as the weight loss which resulted from drying. For sodium, potassium and chloride analysis, dried tissues in known amounts were placed in vitreosil crucibles and ashed over night at 450° to 500° C. in a muffle furnace. Dry samples to be analyzed for chloride were moistened with a saturated solution of sodium carbonate and those to be analyzed for sodium and potassium with concentrated sulfuric acid to prevent volatilization of chloride, and sodium and potassium, respectively. The tissues to be analyzed for chloride were ashed in a separate muffle furnace from those analyzed for sodium and potassium in order to prevent cross contamination. Ashed tissues were analyzed for chloride by the Van Slyke and Hiller modification of the Sendroy technique (10). The ashed tissues to be analyzed for sodium and potassium were dissolved in 1 N sulfuric acid and diluted with distilled water and appropriate equantities of lithium nitrate. The resulting solution was then analyzed for sodium and potassium in an internally standardized flame photometer. The fat content of bone and muscle was determined by the use of a soxhlet apparatus. Blood contamination of muscle was determined after the method of Eichelberger and Roma (11). That the calcium of bone does not interfere with the determination of sodium and potassium in a flame photometer was demonstrated by the use of an aqueous solution of sodium and potassium chloride in the concentration obtained in bone analysis. Duplicate aliquots were removed and calcium was added to one in an amount calculated to be the concentration present in solutions analyzed for bone sodium and potassium. The electrolyte concentrations in the various aliquots were not found to be significantly different. The electrolyte content of tendon is expressed as mEq. per Gm. of dry tissue, those of cortical bone as mEq. per Gm. of fat free, dry tissue, and the values in muscle as mEq. per Gm. of blood free, fat free, dry tissue. The water content of all tissues is expressed as Gm. per Gm. of wet tissue.

Plasma was analyzed for chloride by the Van Slyke and Hiller modification of the Sendroy technique (10). Sodium and potassium concentrations in plasma were determined by the use of an internally standardized flame photometer. Inulin was analyzed by the resorcinol method of Schreiner (12).

RESULTS

In five of the nine DCA treated monkeys studied, the body weight and volume of distribution of inulin were measured before and after DCA treatment (Table I). No significant change in body weight occurred as a result of the treatment. Each of the five animals studied presented significant expansion of the inulin space. Post-treatment volumes averaged 34 per cent (25

TABLE II

Plasma electrolyte concentrations before and after DCA administration

Monkey number		Na	K	Cl
			mEq./L.	
19	Control	141.8	3.3	111.7
	DCA	140.0	3.5	113.8
23	Control	142.0	3.6	114.3
	DCA	139.4	3.8	110.0
25	Control	140.8	4.4	117.3
	DCA	141.6	3.9	114.8
29	Control	139.0	3.6	107.5
	DCA	142.0	3.4	110.0
39	Control	142.0	3.0	109.1
	DCA	134.5	3.0	102.2
44	Control	135.0	3.1	105.0
	DCA	140.0	3.7	112.4
45	Control	138.0	4.2	102.8
	DCA	138.0	4.2	109.8
46	Control	134.2	4.0	108.4
	DCA	135.7	4.7	112.6

TABLE III

The values of water and electrolyte contents of muscle, bone and tendon of normal and DCA treated monkeys

	Monkey	Muscle†				Bone‡				Tendon§			
		Water*	Na	K	Cl	Water*	Na	K	Cl	Water*	Na	K	Cl
		Gm./Gm.	*mEq./Gm.*	*mEq./Gm.*	*mEq./Gm.*	*Gm./Gm.*	*mEq./Gm.*	*mEq./Gm.*	*mEq./Gm.*	*Gm./Gm.*	*mEq./Gm.*	*mEq./Gm.*	*mEq./Gm.*
	7	0.777	0.1037	0.4403	0.0712								
	8	0.763	0.1043	0.4330	0.0546								
	10	0.765	0.1175	0.4475	0.0733								
	11	0.779	0.1163	0.4544	0.0662								
	22	0.757	0.0950		0.0576	0.120	0.3235	0.0047	0.0227	0.576	0.2094	0.0208	0.2315
Normal	30	0.793				0.129	0.3110	0.0063	0.0250	0.583	0.2064	0.0278	
monkeys	34	0.765		0.4161	0.0651	0.122			0.0230	0.577			0.2274
	40	0.765	0.0907	0.4529	0.0609	0.125	0.3072	0.0062	0.0218	0.562	0.2280	0.0315	0.2226
	41	0.770		0.4398	0.0781	0.112	0.3100	0.0100	0.0206	0.556	0.2070	0.0328	0.2271
	43	0.783	0.1083	0.4610	0.0628	0.109	0.3000	0.0077	0.0246	0.599	0.2240	0.0308	0.2393
	48	0.790	0.0957			0.104	0.3200	0.0083	0.0203	0.587	0.2092	0.0203	0.2055
	49	0.759	0.0903			0.111	0.3068	0.0094	0.0211	0.585	0.2072	0.0215	0.2207
	Average	0.772	0.1023	0.4431	0.0655	0.117	0.3112	0.0075	0.0224	0.578	0.2130	0.0265	0.2250
	S.D.	0.011	0.0097	0.0133	0.0072	0.008	0.0075	0.0016	0.0016	0.012	0.0083	0.0050	0.0097
	19					0.117	0.3451	0.0121	0.0202	0.572	0.1902	0.0305	0.2052
	23	0.762	0.1171	0.4475	0.0721	0.116	0.3194	0.0075	0.0228	0.580	0.2087	0.0240	0.2058
	25	0.765	0.1096	0.4312	0.0732	0.115	0.3155	0.0131	0.0211	0.561	0.2321	0.0290	0.2314
DCA	29	0.753	0.1915	0.4709	0.1050	0.122	0.3305	0.0100	0.0192	0.570	0.1803	0.0152	0.1942
treated	39	0.743	0.1409	0.3527	0.0908	0.122	0.3200	0.0075	0.0246	0.564	0.2009	0 0222	0.2131
monkeys	44	0.755	0.1331	0.3613	0.0667	0.127	0.3217	0.0073	0.0211	0.569	0.2025	0.0304	0.2082
	45	0.764	0.1007	0.4036	0.0552	0.130	0.3138	0.0088	0.0200	0.586	0.1900	0.0224	0.2313
	46	0.760	0.1410	0.4134	0.0870	0.113	0.3090	0.0066	0.0222	0.587	0.2167	0.0285	0.2337
	50	0.765	0.1340	0.4832	0.1154	0.134	0.3057	0.0088	0.0210	0.573	0.1958	0.0258	0.2087
	Average	0.757	0.1338	0.4205	0.0837	0.122	0.3201	0.0091	0.0214	0.573	0.2020	0.0253	0.2175
	% change	−2.0	+30.8	−7.4	+27.8	+4.7	+2.1	+21.3	−4.4	−0.9	−5.1	−4.5	−3.3
	t	3.13	3.18	1.292	2.514	1.285	1.698	1.507	1.213	0.890	2.015	0.4575	1.156
	p	0.005	0.005	0.100	0.010	0.100	0.050	0.080	0.100	0.200	0.030	0.300	0.150

* In all tissues, water is expressed as Gm. per Gm. of wet tissue.
† Electrolytes are expressed as mEq. per Gm. of fat free, blood free, dry tissue.
‡ Electrolytes are expressed as mEq. per Gm. of fat free, dry cortical bone.
§ Electrolytes are expressed as mEq. per Gm. of dry tissue.

to 42 per cent) beyond those obtained prior to DCA administration. The plasma concentrations of sodium, potassium and chloride in eight monkeys were not significantly altered by the treatment (Table II).

A comparison of water, sodium, potassium and chloride contents of muscle in normal and DCA treated animals is presented in Table III. Only a small diminution occurred in water content. The 30 per cent rise in sodium content (0.03 mEq. per Gm.) in the treated group represents a considerable increment above the normal. This change was accompanied by a similar increase in chloride content of 0.018 mEq. per Gm. which averaged 27 per cent. The validity of these changes is attested to by t values of 3.18 and 2.514 and p values of 0.005 and 0.01 for sodium and chloride, respectively. The fall in potassium content averaged 0.04 mEq. However, significant changes occurred in only half of the animals. A comparison of the electrolyte and water composition in bone of normal and DCA treated monkeys revealed small changes of questionable significance (Table III). Similarly, the tendon in both groups showed no noteworthy difference (Table III).

No demonstrable change occurred in the glomerular filtration rate as a result of DCA administration.

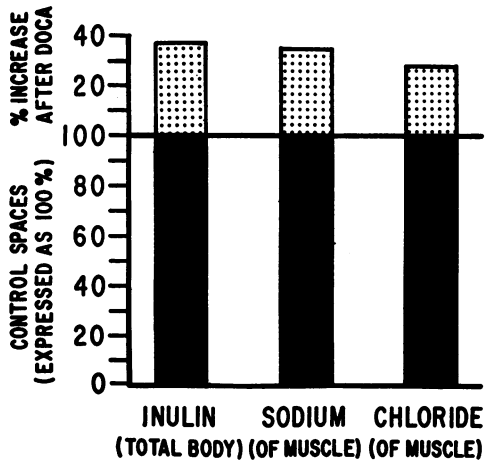

FIG. 1. THE EFFECT OF DCA ON FLUID AND ELECTROLYTE SPACES

The black portions of the bar graphs represent the total body inulin spaces and the calculated sodium and chloride spaces of muscle in the control animals expressed as 100 per cent. The stippled areas represent the per cent increase in those spaces following DCA administration.

DISCUSSION

The mean expansion of the inulin space of 34 per cent compared reasonably well with that noted after the administration of DCA, cortisone, and adrenocorticotropic hormone (ACTH) in dogs and man, respectively (1, 2). The 30 per cent increment in sodium and chloride content of muscle without any change in the plasma electrolyte composition suggests a comparable expansion in the extracellular fluid phase of muscle. The similarity between this expansion and that detected with the inulin space (Figure 1) argues that a true increase in extracellular volume had occurred. It is difficult to explain the increased quantity of salt in the muscle by any other hypothesis. The quantity of salt contained in the low salt diet throughout this five day period could account for only one-fourth of such an expansion. That the sodium content of muscle increased somewhat more than the chloride content may be attributed to the shift of a fraction of the retained sodium into cells to replace some of the lost potassium. These experiments, then, support the conclusion that the administration of DCA effects a transfer of sodium and chloride into the fluid phase of the extracellular compartment. The absence of comparable changes in bone and tendon electrolyte composition indicates that this redistributed electrolyte did not derive from these solid phases of the extracellular compartment. Some have suggested that the gastrointestinal tract might serve as a source of salt and water (1, 2), and these experiments indirectly suggest that such may be the case.

The slight fall in the total muscle water content suggests that the intracellular volume of muscle decreased after DCA administration. The outward shift of cell water may have occurred in association with the slight potassium loss and/or in order to maintain extracellular iso-osmolarity. The latter hypothesis would imply that the salt was transferred into the extracellular phase of muscle in relatively hypertonic concentrations.

The absence of a marked fall in muscle and plasma potassium and the meager degree of extracellular alkalosis are somewhat different from the typical responses described by others after DCA administration (13, 14). Most of the experimental work was performed in animals

treated with the hormone for prolonged periods and maintained on normal or even high salt intakes. It has been shown by others that DCA administration in animals or man maintained on salt-free diets causes far less urinary potassium loss (15). The meager degrees of potassium deficiency and extracellular alkalosis are, therefore, probably attributable to the marked salt restriction and the short period of hormonal treatment.

SUMMARY

1. The administration of DCA produced an increment in inulin space in monkeys maintained on a low salt diet.

2. Proportionate increases in the sodium and chloride spaces of muscle were also observed.

3. The sodium and chloride transferred to the extracellular fluid did not derive from bone or tendon.

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