Effect of Mineralo- and Glucocorticoids on Fasted Adrenalectomized Dogs Subjected to Electroshock.* (25773)

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A basic physiological difference exists between adrenal mineralo- and glucocorticoids in that the former require an exogenous source of food and water to exhibit life-maintaining properties in adrenalectomized (adx) dogs, whereas the latter do not demand either but are capable of restoring normal activity and vigor to the starved, dehydrated animal despite continued withholding of fluid and nutrients during recovery period(1-3). The following experiments were designed to explore further this significant difference between the 2 steroid types with special reference to the role of glucocorticoids in restoring to normal health, fasted adx dogs exhibiting severe symptoms of insufficiency as a result of stress induced by electroshock.

Methods. Electroshock was employed as a convenient stressor to induce circulatory failure in adx dogs. Animals adequately maintained by daily i.m. injections of 0.5 mg DCA were subjected to severe electroshock; steroid was withheld 2-3 days and the dog fasted 24 hours before applying electric current. Shock was produced by passing 150-180 milliamperes of electric current through the brain for 0.2 second and the procedure repeated within 30 minutes in most cases. The animals exhibited convulsions, muscle rigidity, salivation and loss of consciousness. These manifestations were accompanied by micturition and defecation. Gross symptoms disappeared within 5-10 minutes. Blood for sampling (37 cc) was withdrawn 15-30 minutes later, the urinary bladder drained, rinsed with distilled water and the dogs placed in metabolism cages without access to food or water for an additional 48-72 hours. Non-adx animals are relatively insensitive to rapidly repeated, severe electroshock; the initial reaction although violent, is evanescent, recovery is complete and there are no after effects. Response of the fasted adx dogs maintained on DCA to application of electrical current to the brain is quite different. They rapidly recover from the convulsive seizure then slowly develop a shock-like syndrome during the ensuing 24-48 hours which terminates fatally in untreated animals.

Results. I. Failure of mineralocorticoids (DOC), to revive fasted adrenalectomized, electroshocked dog from circulatory failure. Pertinent data are presented in Tables IA and IIA. During the 15-30 minute interval after shock mean arterial pressure declined. Sharp rises usually occurred in blood sugar and blood urea nitrogen of DOC-treated animals. Hemoconcentration was present and acidosis evident, as indicated by fall in blood pH and CO_2 content. There was reduction in plasma volume and an increase of plasma Na which in Dog 1, later attained an extreme value. During the following 24 hours these deviations from control values occasionally became more marked. At termination of the 24th hour after administering electroshock, blood was withdrawn for sampling; treatment with solubilized DOC was then started and 30-50 mg were given i.v. in divided doses; Dog 3 was exceptional in that mineralocorticoid was given 5 hours after shock. The steroid failed to alleviate symptoms or improve the clinical condition. Plasma K continued to rise in Dog 1 whereas renal elimination of this ion practically ceased Severe symptoms of hyperkalemia (*e.g.*, loss of control of the hind legs) were present. This animal's condition was so serious the experiment was terminated. He was restored to normal activity within 6 hours by infusion of 250 cc of 1% NaCl plus 2% of Na HCO_3 and 10 mg of 2-methyl-9α-fluorohydrocortisone. This therapy provoked K

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TABLE I. Effect of Severe Electroshock on Active, Vigorous, Adrenalectomized Dogs Maintained on Desoxycorticosterone.

Time (hr), condition of animal		Body wt, kg	BP, mm Hg	Blood urea N, mg %	Hb, g %	Hmct, %	RBC 10^6, mm^3	Blood sugar, mg %	pH	Plasma CO_2 vol, %	Plasma cc/kg	Vol, % change	Steroid, mg 24 hr
A. Failure of mineralocorticoid (DOC) to prevent circulatory failure in electroshocked adrenalectomized dogs deprived of food and water. Dogs 1-3.													
Initial	N	19.3	116	23.4	12.4	38.5	6.11	79	7.32	44.3	53.9		
15 min.	S	19.1	63	38.6	16.2	46.6	7.92	90	7.15	34.9	30.0	−44.3	
24 hr	S	18.9	79	67.6	16.0	44.7	7.29	71	7.21	32.5	29.7	−44.8	30*
48	S	18.4	42	87.5	16.7	46.1	7.21	70	7.23	34.6	30.2	−43.9	
Initial	N	26.7	130	24.0	13.7	38.8	5.62	79			43.9		
30 min.	S	26.5	95	24.1	15.6	45.4	6.34	104			36.6	−16.6	
24 hr	S	25.4	92	30.2	15.6	45.6	6.32	80			25.9	−41.0	50*
48	S	24.8	80	48.0	15.4	43.8	6.14	92			28.6	−34.8	100‡
72	R	24.2	96	28.2	13.8	39.7	5.79	126			44.3	+71.0	
Initial	N	23.1	122	21.1	15.4	40.0	5.73	76			46.3		
5 hr	S	22.0	90	29.1	14.7	39.5	5.84	95			34.1	−26.3	50†
24	S	21.0	70	40.4	13.7	38.1	5.76	91			34.0	−26.5	100‡
48	R	21.3	90	21.9	11.7	34.6	4.32	108			45.5	+33.8	
B. Restoration of electroshocked adrenalectomized dogs to normal with glucocorticoids despite lack of food and water. Dogs. 4-6.													
Initial	N	21.5	110	19.7	11.5	32.9	4.99	86	7.38	51.8	49.3		
15 min.	S	21.3	95	28.3	12.9	36.3	5.60	89	7.00	41.0	42.8	−13.1	
24 hr	S	20.6	87	29.0	12.8	33.1	5.13	80	7.31	47.9	37.6	−23.7	13§
48	R	19.7	106	22.3	9.9	26.4	4.42	95	7.41	46.8	57.2	+52.7	
Initial	N	20.2	112	23.1	10.4	30.1	4.50	86	7.33	44.7	48.4		
15 min.	S	20.0	98	21.4	12.8	36.3	6.08	96	7.20	34.8	42.5	−12.7	
24 hr	S	19.3	78	26.5	12.9	37.0	5.61	77	7.36	44.6	34.7	−28.3	50‖
48	R	18.2	110	24.1	10.1	29.9	4.75	100	7.32	40.2	43.0	+23.1	
Initial	N	27.1	102	20.2	11.7	31.1	4.53	84	7.32	47.7	44.7		
15 min.	S	26.6	100	22.3	12.8	35.4	5.80	96	7.14	25.8	33.8	−24.3	
24 hr	S	25.5	80	25.5	13.6	36.1	5.18	75	7.32	46.4	32.1	−28.1	50‖
48	R	24.7	88	18.8	11.1	29.8	4.12	98	7.37	42.6	46.6	+45.1	

* DOC i.v. in 2 divided doses 24 hr after electroshock.
† *Idem* 5 hr after electroshock.
‡ 1-dehydrohydrocortisone hemisuccinate i.v. in 2 doses 24 or 48 hr after electroshock.
§ 2-methyl-9 α-fluorohydrocortisone i.v. in 2 doses 24 hr after electroshock.
‖ 50 mg 1-dehydrohydrocortisone hemisuccinate i.v. in 2 doses 24 hr after electroshock.

− = Decrease in plasma vol following electroshock and DOC therapy. + = Increase in plasma vol after glucocorticoid injections. N = Normal. S = Shock. R = Recovery.

diuresis which reduced plasma K from 8.93 to 4.6 meq/l. Dogs 2 and 3 recovered rapidly following injection of glucocorticoid despite continued deprivation of food and water. Large amounts of K were excreted accompanied by reduction in plasma K. Table II.

II. Restoration of fasted electroshocked adx dog to normal health with glucocorticoids. Alterations in blood pressure, blood constituents and plasma volume produced by electroshock at 15 minutes and 24 hours differed only in degree from those discussed for the DOC series (Tables IB and IIB). The changes were milder since near loss of one of the DOC-treated dogs showed the necessity for initiating restorative measures before serious symptoms developed. Glucocorticoids were given i.v. in divided doses beginning 24 hours after electroshock and continued until recovery which was complete 24 hours later. Unlike the DOC-treated dogs, these animals showed a prompt return to control or near control values of arterial pressure; hemoconcentration was much reduced and striking increases in plasma volume occurred. Plasma Na, Cl and K remained at or near levels observed before therapy but in view of the expansion of plasma volume the quantity of these ions must have increased. Fluid and electrolyte diuresis appeared with renal excretion of enhanced quantities of Na, Cl and K in those dogs receiving 1-dehydrohydrocortisone but retention of Na and Cl and elimination of K occurred in the one animal injected

TABLE II. Plasma and Urine Electrolytes of Fasted Electroshocked Adrenalectomized Dogs.

Time (hr), condition of animal		Plasma electrolytes, meq/l Na	Cl	K	Urine vol, cc	Urine electrolytes, meq Na	Cl	K	
A. Treated with mineralocorticoid. Dogs 1-3.									
Initial	N	144.0	117.9	4.40					
15 min.	S	146.0	110.8	4.62					
24 hr	S	150.0	114.9	7.72	120	6.7	11.3	2.53	*
48	S	162.0	118.2	8.93	24	2.4	4.2	1.34	
				Total	144	9.1	15.5	3.87	
Initial	N	141.0	111.0	5.03					
30 min.	S	142.0	109.4	5.03					
24 hr	S	143.0	111.5	5.46	340	40.12	32.6	6.08	*
48	S	147.0	115.9	5.20	250	3.28	2.78	14.83	‡
72	R	141.0	119.2	4.38	250	1.42	.56	29.86	
				Total	840	44.82	35.9	50.77	
Initial	N	141.0	111.1	4.64					
5 hr	S	141.0	111.1	4.66					†
24	S	141.5	112.8	5.01	89	5.3	4.0	9.6	‡
48	R	142.0	115.5	3.73	270	2.3	4.2	41.7	
				Total	359	7.6	8.2	51.3	
B. Treated with glucocorticoids. Dogs 4-6.									
Initial	N	147.5	119.0	4.06					
15 min.	S	150.0	117.3	4.22					
24 hr	S	150.5	119.7	4.95	220	44.2	34.7	7.0	§
48	R	152.0	116.9	4.38	425	5.3	16.4	48.6	
				Total	645	49.5	51.1	55.6	
Initial	N	148.0	116.8	4.06					
15 min.	S	150.5	117.9	4.47					
24 hr	S	151.0	117.6	4.93	222	28.4	26.2	14.1	‖
48	R	149.0	122.1	4.95	370	47.0	26.3	37.4	
				Total	592	75.4	52.5	51.5	
Initial	N	144.0	116.0	4.48					
15 min.	S	147.0	115.0	4.62					
24 hr	S	147.5	115.9	4.97	205	43.1	40.2	12.6	‖
48	R	147.5	112.8	4.60	675	93.9	71.0	54.4	
				Total	880	137.0	111.2	67.0	

* 30-50 mg DOC in 2 divided doses 24 hr after electroshock.
† 50 mg DOC in 2 divided doses 5 hr after electroshock.
‡ 100 mg 1-dehydrohydrocortisone hemisuccinate i.v. in 2 divided doses 48 hr after shock.
§ 13 mg 2-methyl-9α-fluorohydrocortisone 24 hr after shock.
‖ 50 mg 1-dehydrohydrocortisone hemisuccinate i.v. in 2 divided doses 24 hr after shock.
N = Normal. S = Shock. R = Recovery.

with 2-methyl-9α-fluorohydrocortisone — a steroid which possesses both glucocorticoid and mineralocorticoid activity in marked degree (Table IIB, Dog 4). Urinary loss of Na and K during the 24 hour period of recovery after receiving glucocorticoids was for Dogs 4-6: 5.3, 47.0 and 93.9 meq of Na and 48.6, 37.4 and 54.4 meq of K. Since food and water were unavailable and plasma electrolytes remained elevated whereas the plasma volume had expanded, it seems justifiable to conclude that some of these ions, especially K, were derived from cells accompanied by large volumes of water shifted into the intravascular space. The source of the considerable quantities of Na and Cl poured out in the urine is not so evident, although some apparently were also derived from cells.

Discussion. An immediate response of mammalian species to electroshock is marked disturbance of the electrolyte pattern of the brain cells. K shifts out of the cells and is replaced by Na during the convulsions. When this phase has ceased, a reverse shift of ions and water is initiated and Na and K resume their usual extra- and intracellular positions (4,5). Acidosis, increased plasma Na, decline in plasma volume and rapid redistribution of

TABLE III. Water and Electrolytes Mobilized from Extravascular Sources Following Glucocorticoid Therapy. (Amounts in expanded vascular compartment and urine combined.)

Dog. No.	Water, cc	Na^+, meq	K^+, meq
4	777	60	50
5	483	63	38
6	1007	143	55

body water characterized by contraction of the extracellular space have been reported to occur after electroshock(6-8). All investigators cited comment that the changes enumerated are transitory and rapidly disappear upon cessation of convulsions. However, data in Tables I and II demonstrate that fall in arterial pressure, plasma volume and increased hemoconcentration, induced by electroshock in fasted adx dogs following withdrawal of DCA for several days, are not merely temporary but are changes the untreated animal is unable to reverse spontaneously. Solubilized mineralocorticoids such as DOC and aldosterone when administered i.v. in relatively enormous doses are ineffective for reviving fasted adx dogs from shock or insufficiency whereas glucocorticoids are extremely effective and readily restore activity and vigor to the starved, dehydrated animal prostrate from insufficiency.

Data presented in Tables I and II demonstrate the effectiveness of glucocorticoids in contrast to desoxycorticosterone for reviving these seriously ill animals from the stress of electroshock. Following injection of this type steroid, arterial pressure and plasma volume increased markedly, hemoconcentration was sharply reduced but alterations of plasma K were not a consistent finding. Although the concentrations of plasma Na and Cl did not show significant changes the total quantity of these ions in the intravascular compartment increased considerably (Table III). Since exogenous sources of water and electrolyte were lacking during recovery obviously large amounts of these substances must have been mobilized from extravascular sources and shifted into the *intravascular* compartment. Approximate values for the quantities of water, Na and K mobilized by the glucocorticoid (Dogs 4-6, Tables I and II) are shown in Table III.

The dramatic and rapid recovery of the animals is due, apparently, to 1) activity of glucocorticoids in mobilizing fluid and certain electrolytes from extravascular sites and redistributing them to the intravascular compartment and 2) stimulation of renal mechanism to excrete excess water, Na and K mobilized as a result of administering the steroid. Thus adrenal C_{11} oxysteroids, in contrast to desoxycorticosterone and other mineralocorticoids, appear to be a vital part of the mechanism which maintains the internal water and electrolyte balance of the vertebrate organism. However, the exact role they play in this important function remains unknown.

Summary. Electroshock induces circulatory failure in fasted adrenalectomized dogs maintained on mineralocorticoid. Treatment with desoxycorticosterone is ineffective and animals succumb exhibiting retention of Na, Cl and renal elimination of but small amounts of K. Despite continued fasting, glucocorticoid injections bring about rapid return of normal activity and vigor accompanied by increased arterial pressure, plasma volume, and decreases in hemoconcentration. Plasma Na and Cl concentrations showed little or no changes but the total quantity of these ions in the intravascular compartment increased significantly. The data indicate that C_{11} oxysteroids mobilize large amounts of water and electrolyte from extravascular sources of the adrenalectomized dog prostrate from insufficiency and shift them into the intravascular compartment thereby bringing about dramatic and rapid recovery. Thus glucocorticoids, in contrast to mineralocorticoids, are apparently a vital part of the mechanism which maintains the internal water and electrolyte balance of vertebrate organisms although the precise role they play in this important function is unknown.

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Effect of Reserpine on Adrenalectomized Rats.* (25774)

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Gaunt *et al.*(1) noted that doses of reserpine ranging upwards from 50 μg/kg/day reduced survival time of adrenalectomized rats. This might be due to an increased requirement for cortical hormones or to release of serotonin from tissues(2). Jaques, Mogenson and Fisher(3) showed that hemorrhage occurred readily when adrenalectomized rats were given dicumarol, all dying of hemorrhage while controls all survived. This was explained by the observation(4,5) that interference with any 2 of the 3 major hemostatic lines of defense (blood coagulation, platelet plugging, vascular integrity and response) present an overwhelming hemorrhagic defect. The work of Correll *et al.*(6) and Zucker and Borrelli(7) indicated that platelet serotonin is involved in normal hemostatic mechanisms, and Jaques and Fisher(4) showed that reserpine produced hemorrhage in rabbits subjected to stress. The experiments reported were undertaken to compare hemorrhagic death in adrenalectomized rats treated with reserpine, with that already studied in other experiments using these treatments.

Methods. Adrenalectomized rats were maintained on 0.9% saline and received hydrocortisone (1 mg/100 g/day) for 3 days post-operatively. Treatments were started one week after operation, as follows—reserpine 2 mg/kg intraperitoneally, desoxycorticosterone acetate (DOCA) 2.5 mg/kg daily subcutaneously. The animals were examined daily. Mortality was recorded as number of deaths to the tenth day. A careful autopsy was made.

Results. Groups of approximately 25 rats (adrenalectomized and sham-operated) were divided into subgroups receiving reserpine and no reserpine. The experiment was then repeated with DOCA given at various time intervals. Number of animals, respective treatments, and mortality are shown in Table I.

Adrenalectomy + Reserpine. There was a profound diarrhea and intense gastrointestinal discomfort in animals of Group 1. Half of them died within 6 hours, others died within 24 hours to give a mortality of 80% (16 rats). In every case diarrhea was present. Feces were eliminated and thin mucus kept issuing from the anus. The presence of gross blood in feces and/or intestinal lumen was observed in 25% of the post mortem examinations.

TABLE I. Mortality of Adrenalectomized Rats Treated with Reserpine.

	No.	Died	% mortality
Adrenalectomized + reserpine	20	16	80
Adrenalectomized only	18	3	17
Sham operated + reserpine	25	1	4
Sham operated only	21	1	5
Adrenalectomized DOCA for 8 days, reserpine on 6th day	10	1	10
Adrenalectomized DOCA for 4 days, reserpine on 6th day	10	4	40
Adrenalectomized DOCA for 4 days, control	10	1	10
Adrenalectomized DOCA for 8 days, control	9	2	22
Sham operated DOCA for 8 days, control	7	0	0
Sham operated DOCA for 8 days, reserpine on 6th day	10	1	10

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