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Effect of Prolonged High Sodium Chloride Ingestion and Withdrawal upon Blood Pressure of Dogs.* (18784)

C. M. WILHELMJ, E. B. WALDMANN, AND T. F. MCGUIRE.

From the Department of Physiology and Pharmacology, Creighton University School of Medicine, Omaha, Nebr.

The effect of salt ingestion upon blood pressure of dogs with renal hypertension or with partial renal insufficiency has been studied (1,2) but there seems to be a paucity of information on the effect of excess salt ingestion on normal dogs.

Methods. Three well trained, standardized dogs weighing 14.1, 16.3, and 15.3 kg were used. During the control period which lasted for approximately 2 months, the animals were fed the kennel diet of Nutrena dog food. Blood pressure was determined by the auscultatory method of Allen(3) with certain modifications introduced by the authors(4). During the control and experimental period, blood pressure was determined 6 days each week. The daily values as recorded in Table I are the means of at least 10 consecutive readings. In the *first phase* of excess salt ingestion, salt was mixed with the kennel diet and the animals were allowed water *ad libitum*. In Dogs I, II and III, the amount given was 30, 40 and 40 g daily. These amounts represented approximately 2.1; 2.5 and 2.6 g per kg, respectively. Dog I was kept on this regimen for 205 days; Dog II for 56 days, and Dog III for 154 days. In the *second phase* of excess salt ingestion which followed the first phase without interruption, the animals were given a 2% sodium chloride solution as the sole source of drinking water. This period lasted 49, 49 and 35 days in the 3 dogs and was terminated because of the advent of warm weather and evidences of toxic effects. The total time of excess salt ingestion (Phase I plus Phase II) was 254, 105 and 189 days.

Results. Phase I. The results and the

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TABLE I. Blood Pressure of Dogs on Excess Salt Intake.

Dog	Conditions	Mean	S. D.*	C. V.†	C. R. with control‡	P§	N‖
I	Control	95/50	7.2	7.6	—	—	32
			6.5	13.1	—	—	
	20 g NaCl	107/51	9.7	9	4.6	>.01	20
	Struggle		6.8	13.3	.5	<.50	
	30 g NaCl	115/59	12.4	10.8	6	>.01	16
	Struggle		7	11.9	4.3	>.01	
	30 g NaCl	107/54	8.7	8.1	2.9	>.01	11
	Basal		5.6	10.7	1.92	<.05	
	2% NaCl	104/53	14.7	14.1	3.4	>.01	40
	Drink		9.1	17.2	1.6	<.1	
	After NaCl	78/37	6.4	8.2	8.5	>.01	18
	Stopped		6.8	18.4	6.6	>.01	
II	Control	98/55	5.5	5.6	—	—	44
			7.8	14.2	—	—	
	30 and 40 g NaCl	117/57	9.8	8.4	6.9	>.01	14
	Struggle		10.2	17.8	.6	<.50	
	40 g NaCl	97/51	9	9.2	.7	<.5	24
	Basal		6	11.8	2.4	>.02	
	2% NaCl	103/49	13.5	13.1	2.16	>.01	39
	Drink		10	20.3	3	>.01	
	After NaCl	84/41	6.6	7.9	8	>.01	18
	Stopped		4.8	11.6	8.6	>.01	
III	Control	98/50	5.7	5.8	—	—	40
			6.3	12.5	—	—	
	30 and 40 g NaCl	118/50	21.1	17.9	3.74	>.01	10
	Struggle		5.1	10.3	0	—	
	40 g NaCl	101/45	6	6	1.37	<.10	9
	Basal		6.9	15.2	2	<.05	
	2% NaCl	98/43	21.2	21.7	0	—	28
	Drink		7.9	18.4	3.9	>.01	
	After NaCl	82/41	5.8	7.1	9.1	>.01	15
	Stopped		7	17	4.4	>.01	

* Std. dev. of mean.
† Coefficient of variation.
‡ Critical ratio of mean experimental systolic and diastolic pressure compared with control.
§ Probability that observed changes in the mean are not due to chance.
‖ No. of daily blood pressure determinations in each period.

statistical analyses are shown in Table I. Any change in the mean values which was equal to or greater than the 5% level of confidence ($P \geqq .05$) was considered significant. Each of the 3 dogs showed a similar pattern of reaction which could be divided into 2 periods as follows: (A) *The period of struggle.* Immediately after starting the excess salt ingestion the blood pressure began to show markedly increased daily variations, which were more pronounced in the systolic than in the diastolic pressure. The daily weight also began to show wide fluctuations sometimes as much as 1.5 kg in 24 hours, but the mean weight for any period was usually insignificantly different from the control weight. During this period of struggle, the mean systolic pressure was significantly elevated above the control value in all dogs. In only one dog, however, (Dog I on 30 g) was the diastolic pressure significantly elevated. The duration of the period of struggle was variable, lasting from 9 to 21 days. (B) *The salt basal period or period of compensation.* Following the period of struggle the pressure began to show smaller daily fluctuations, and the previously elevated systolic pressure declined. These changes were interpreted as an adaptation or compensation to excess salt intake. As soon as adaptation occurred the administration of excess salt was continued and the animals were subjected to a second type of stress, namely, confinement in a cage treadmill, which revolved between one and two miles per hour. They were kept in this cage for many periods ranging from 3 to 18

hours daily. The details of these experiments are not included in this paper. It will suffice to say that the initial effect of the second stress was a great increase in blood pressure. For example, following two consecutive nights in the revolving cage treadmill the blood pressure of Dog III rose to 215/80 and it required 10 days to return to the previous level, when this stress was discontinued. Continuation of the second stress, however, resulted in adaptation and the increase in blood pressure became small or insignificant.

Phase II (2% NaCl as drinking water). The salt water was well tolerated and the intake, which varied with the temperature, ranged from 500 to 3000 cc in 24 hours. The effect upon blood pressure was surprisingly small. In all 3 dogs, it differed but slightly from that during the salt basal or compensatory period. The daily fluctuations in pressure were greater than in the period of struggle of Phase I as shown by the increased coefficients of variation. Body weight fluctuated markedly but the mean changes for the period were small. The results obtained in Phases I and II were clearly indicative of a progressively increasing adaptation to the ingestion of excess salt.

Phase III (After discontinuation of excess salt intake). When excess salt administration was suddenly stopped, all 3 dogs immediately showed a marked and highly significant decrease in both systolic and diastolic pressure below the control level which persisted for at least 3 weeks. The coefficients of variation for the systolic pressure decreased and approximated the control values.

A fourth dog was recently given 40 g of sodium chloride daily with the food for 18 days and then given 2% sodium chloride solution to drink for 57 days (a total of 75 days on excess salt). At the end of 57 days of drinking 2% saline the animal became violently ill and the experiment was terminated. The blood pressure of this dog showed less change during the period of excess salt ingestion than was observed on the other 3, but when excess salt ingestion was stopped the blood pressure failed to drop below the control value. Either the period of excess salt ingestion was too short or there are individual differences in the ease with which this phenomenon can be induced.

Discussion. It is obvious that sustained hypertension cannot be produced in normal dogs by the ingestion of excess salt, probably because the dog kidney has phenomenal ability to eliminate excess salt(5). The same observation has been made by Allen(13). The increases in the coefficients of variation suggest that fluid and mineral equilibrium was maintained by virtue of an intense struggle. Eventually the adaptive mechanisms became more efficient and the salt basal or compensation pressures were established, fluctuations in pressure, as indicated by the coefficients of variation then approached the control level. Saperstein *et al.*(6) have pointed out that when excess salt is ingested, but the animal allowed water *ad libitum,* the fluid intake may become so high that the animal is able to excrete the excess salt. They state that fluid intake should be limited when excess salt is given and suggest that this be done by giving 2% saline solution as the sole source of drinking water. In rats this causes definite hypertension(6,7). In the present studies, Dogs I, II, and III had been on a high salt intake for 205, 56 and 154 days before 2% saline ingestion was started and the adaptive mechanisms had become so perfected that elevation of blood pressure above the salt basal or compensatory level was entirely prevented in Dogs I and III. In Dog II there was a significant elevation of systolic pressure above the salt basal value ($P > .05$). This may be due to the fact that this dog had been on excess salt ingestion for a much shorter period than the other 2 dogs, hence the adaptive mechanisms were not as highly developed.

The marked decrease in blood pressure following the sudden withdrawal of salt was an unexpected finding, the exact cause is unknown but we suggest the following hypothe-

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13. Allen, F. M., Personal communication.

sis: During the prolonged period of high sodium ingestion, the secretion of mineralocorticoids from the adrenal cortex dropped to low levels, since there was no need for conservation of sodium. When excess sodium administration was suddenly stopped, the familiar phenomenon of glandular inertia occurred and mineralo-corticoid secretion remained low (in these experiments for at least 3 weeks). This hypothesis necessitates two other implications, (1) that mineralo-corticoids are normally responsible for maintaining blood pressure at a higher level than it would be in their absence and (2) that excess salt ingestion *per se,* was responsible for maintaining the blood pressure above the post withdrawal level. It is important to emphasize that during the period of low blood pressure, the animals showed no gross evidence of adrenal insufficiency. The above hypothesis is supported by direct evidence obtained by cytological studies of the adrenal cortex. Deane, Shaw, and Greep(10), Selye and Stone(11), and Bacchus(12) have shown that when the sodium-potassium ratio is raised there is evidence of decreased activity in the glomerular zone. The administration of desoxycorticosterone produces similar changes. Lowering of the sodium-potassium ratio brings about changes indicative of increased activity in the glomerular zone.

It may be significant that the blood pressure level after sudden salt withdrawal was of the same order of magnitude as the stable fasting level which we have found in dogs(4). Selye (8,9) has postulated that the amount of adaptation energy is limited so that when an animal has become resistant to one type of stress, it is highly susceptible to a second stress. In the present experiments prolonged confinement (up to 18 hours per day) in a slowly revolving cage treadmill was used as a second stress. The first effect was a marked and sometimes prolonged elevation of systolic and diastolic pressure, but as the second stress was continued, the response became progressively less, hence adaptation to the second stress was marked even when the first stress was continued. It is possible that the second stress was not of sufficient intensity to elicit the effect described by Selye. It has not been possible to standardize the response to the revolving cage treadmill with sufficient accuracy to state whether dogs on high salt intake are more sensitive to this type of stress than normal dogs.

Summary. 1. Three well trained standardized dogs were given excess sodium chloride in the diet in amounts approximating 2.5 g per kg weight for 205, 56 and 154 days respectively. The first effect was a marked increase in the daily variations in blood pressure and a small but significant elevation of the systolic pressure. In only one dog was the diastolic pressure elevated. As excess salt ingestion was continued there was evidence of increasing adaptation characterized by a drop in the previously elevated systolic pressure. Adaptation finally became so highly developed that when the salt stress was increased by giving 2% saline solution as the sole source of drinking water, 2 dogs showed no additional elevation in systolic pressure while one showed a small but significant elevation. 2. After adaptation to salt was complete, a second stress caused elevation of both systolic and diastolic pressure but continuation of the second stress led to adaptation. 3. The sudden withdrawal of excess salt after administration for 254, 105 and 189 days, respectively, was quickly followed by a marked and highly significant fall in both systolic and diastolic blood pressure, which persisted for at least 3 weeks. A possible cause for this drop in pressure is discussed.

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