of 5-iodo-2′-deoxyuridine was resistant to it *in vivo* although this resistant virus induced normal amounts of thymidine kinase in mutant LM cells deficient in thymidine kinase. A different strain deficient in thymidine kinase was susceptible to 5-iodo-2′-deoxyuridine *in vivo*, presumably because 5-iodo-2′-deoxyuridine was phosphorylated by cellular thymidine kinase. Viral resistance to 5-iodo-2′-deoxyuridine, unlike the resistance of cancer cells, cannot depend solely on the loss of thymidine kinase inducing ability.

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Received March 19, 1965. P.S.E.B.M., 1965, v120.

Sodium and Potassium Intake, Blood Pressure, and Pressor Response to Angiotensin.* (30434)

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In several forms of experimental hypertension the induced elevation in blood pressure is related to the amount of sodium(1-4) and potassium(5,6) in the diet. In addition, the intake of both these ions influences the rate of aldosterone secretion(7,8), while only sodium affects the granularity of the juxtaglomerular cells(9). The studies of Dahl and Love(10) suggest that increased consumption of salt may be an etiological factor in the development of essential hypertension. Moreover, it has been shown repeatedly that a low sodium diet can often lower the blood pressure of hypertensive patients(11,12). The work of Tobian(13,14) and others(15, 16) on experimental animals suggests an increase in intracellular potassium, sodium, and water occurs in the vascular smooth muscle of hypertensive animals. The exact mechanisms whereby sodium and potassium influence blood pressure are not known. One possibility might involve an alteration in vascular responsiveness to circulating pressor agents. The present paper describes the effects of varying the concentrations of dietary sodium and potassium on the pressor sensitivity to angiotensin in rats.

* This work was supported by Grants HE-01275 and HE-05741 from Nat. Inst. Health, and by Mrs. Richard C. duPont.

Methods. Male Sherman rats weighing 90 to 130 g were divided into 8 groups of 8 rats each plus a control group of 16 rats. For approximately 8 weeks they were fed diets which differed only in the concentrations of sodium and potassium. The diets, prepared by General Biochemicals, Chagrin Falls, Ohio, were as follows:

Diet	Sodium	Potassium
Control	.25%	.56%
High Na	3.01	.52
Low Na	0	.65
High K	.25	4.19
Low K	.60	0
Low Na - Low K	.025	.004

In addition, 1% NaCl, 1% KCl, or 1%

NaCl + 1% KCl replaced the drinking water in some experimental groups (Table I).

Blood pressure was taken at the beginning and end of the 8-week period. The rats were kept at 39°C and lightly anesthetized with ethyl ether. The pressure in an inflatable cuff on the tail was recorded directly on a Sanborn kymograph. As the pressure in the cuff was decreased below the systolic level, the arterial pulse wave was recorded simultaneously from a Beckman pressure transducer placed just distally to the cuff. The pressure was read at the onset of the first pulse deflection, and the highest consistent reading obtained before the animal awoke from anesthesia was taken as the final value.

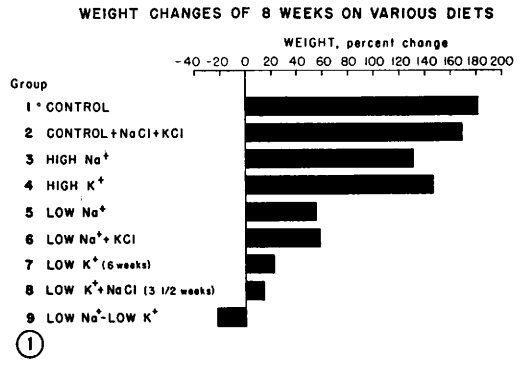
TABLE I.

Group	Diet	Fluid intake	No. of survivors	BP* (mm Hg) Initial	BP* (mm Hg) Final	Weight (g) Initial	Weight (g) Final	Angio dose/100 mg (μg)	Pressor response range‡ (mm Hg)	"Pressor response" (mm Hg)	Significance
(1)	Control	H_2O	10	112	107	102	292	.0035	14-21	20	—
(2)	"	NaCl + KCl	6	121	114	124	328	.0032	15-22	20	NS
(3)	High Na	H_2O	4	105	118	124	286	.0038	23-32	31	$P < .01$
(4)	" K	"	5	119	118	110	272	.0036	17-24	23	NS
(5)	Low Na	"	7	118	106	109	169	.0060	10-16	14	$P < .01$
(6)	" "	KCl	4	114	109	109	172	.0058	7-16	14	$P < .01$
(7)†	" K	H_2O	3	125	97	117	143	.0073	10-15	13	$P < .01$
(8)†	" "	NaCl	4	117	101	110	125	.0080	8-23	17	NS
(9)	Low Na +low K	H_2O	7	113	112	124	95	.0106	17-22	21	NS

* Initial and final blood pressure readings refer to those taken by the indirect method at beginning and end of the usual 8 wk feeding period.
† Group (7) received diet for only 6 wk and group (8) for 3½ wk.
‡ Pressor response range is the range of all the increments in blood pressure observed in all animals of each group. The "pressor response" is defined as the mean of the 3 greatest increments observed in each animal. Avg "pressor response" for each group is given.

Pressor response to angiotensin was determined as follows. The rats were anesthetized with pentobarbital in doses of 3.5 to 8.8 mg per 100 g body weight. Vagectomy and blocking agents were not used. Changes in mean arterial pressure were recorded directly on a Sanborn kymograph from a cannula in the carotid artery. 0.01 μg of synthetic angiotensin (Hypertensin—Ciba) was injected into the jugular vein. The animals received from 4 to 9 injections. Each injection was given 5 minutes after a return to the baseline pressure level. In numerous control studies we found that variations in body weight between 100 and 300 g did not alter the pressor response to any given dose of angiotensin, and that 0.01 μg produced an average increment in blood pressure of 20 mm Hg with good reproducibility. Because some of the less healthy animals on the experimental diets were unable to tolerate the greater number of injections necessary to construct dose response curves, we obtained more reproducible results by injecting a single dose of 0.01 μg which produced an increment in the middle of the response range. The final "pressor response" was determined as the average of the 3 highest increments in blood pressure following injections of 0.01 μg of angiotensin.

Results. Weight change and mortality. The effects of the various diets on weight gain are summarized in Fig. 1 and Table I. Animals on the high sodium and high potassium diets grew almost as well as the controls. There was noticeably less weight gain in the low sodium and low sodium + KCl groups though all the surviving animals in these latter two groups appeared healthy. The low sodium-low potassium group had no increase in mortality rate, but several of these rats appeared unhealthy, and all lost weight. All but one of the original group of low potassium rats died before the end



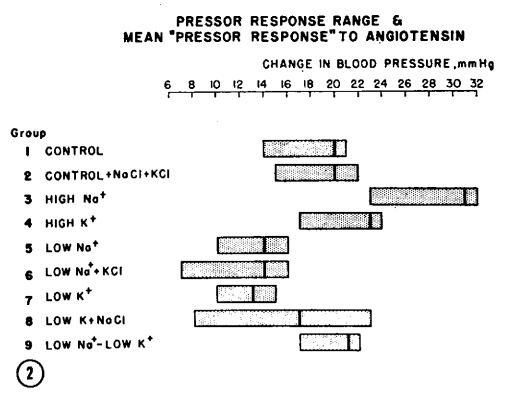


FIG. 1. Weight changes of groups of rats maintained on diets of various electrolyte content for 8 weeks.

FIG. 2. Range of all blood pressure increments in response to a standard dose of 0.01 μg of angiotensin is presented for animals on various diets. Cross bar represents mean "pressor response" for each group, as defined in text.

of 8 weeks. Three more which were placed on this diet for 6 weeks gained weight poorly. All the rats on the low potassium + NaCl diet died within 6 weeks. Eight more animals were started, but the experiment had to be terminated after only 3½ weeks because of their very poor condition and minimal weight gain.

Systolic blood pressure. The changes in blood pressure are also summarized in Table I. The low potassium diet produced a significant decrease in blood pressure ($P<0.01$). However, on a diet deficient in both sodium and potassium there was no change in blood pressure. There was a rise in blood pressure of questionable significance on the high sodium diet ($0.1>P>0.05$). None of the other diets produced any significant changes.

Pressor response to angiotensin. The results are summarized in Table I and Fig. 2. The high sodium rats exhibited a significantly greater response to angiotensin than did the controls ($P<0.01$). The high potassium diet, and the control diet with 1% NaCl-1% KCl drinking fluid did not alter the pressor response.

Rats on a diet deficient in both sodium and potassium responded normally to angiotensin. However, pressor response was significantly ($P<0.01$) diminished in animals fed diets in which either sodium or potassium was reduced alone. The addition of 1% KCl drinking fluid to the low sodium diet did not improve the pressor response. Results with the low potassium diet with 1% NaCl drinking fluid added were inconclusive because these animals were on the diet for only 3½ weeks.

Discussion. In Groups 5 through 9 weight gain was considerably less than for Groups 1 through 4. It might be argued that starvation in itself inhibited pressor response. However, the animals in Group 9 maintained a normal blood pressure and responded normally to angiotensin. Freed has shown that control rats starved to a degree comparable to our animals maintain a normal blood pressure(17). Moreover, the diminished pressor response in Groups 5 through 8 is possibly made more significant because of the fact that these animals actually received a higher dose of angiotensin *per kilo* than did the controls.

Freed first showed that a low potassium diet will lower blood pressure(17) and reduce pressor sensitivity in rats(18). He also found that a diet deficient in both sodium and potassium will not reduce blood pressure (19), but he did not test pressor sensitivity in animals on this diet. Our data agree with these findings.

The most striking observation was the increase in pressor response of the rats maintained on the high sodium diet. This occurred in association with only a minimal rise in resting blood pressure levels. No similar response occurred in the high potassium group or among the control animals which were given 1% NaCl + 1% KCl to drink. A high potassium intake will prevent the de-

velopment of "salt hypertension"(20). It therefore seems that concomitant potassium administration blocks the effect of a high sodium diet on pressor sensitivity. However, this is not absolutely established by our data because the sodium and potassium content of diet No. 2 is not the algebraic sum of diets Nos. 3 and 4.

The finding that an increased sodium intake augments pressor response is compatible with certain data already reported. Vick *et al* found that sensitivity to epinephrine, as measured *in vitro* by contraction of rat aortic strips, could be increased by prior feeding of a 2% sodium diet for 10 weeks(21). Zsoter and Szabo showed that a similar diet increased the sensitivity *in vivo* of mesoappendix vessels to topical epinephrine(22). Raab *et al*(23) reported that sodium restriction reduced pressor sensitivity in hypertensive humans, but Dahl(24) was unable to confirm these findings. Davis *et al* found that pressor sensitivity to angiotensin was reduced in sodium-depleted dogs(25). In man pressor response to both angiotensin and norepinephrine depends on sodium balance (26).

It is of interest that a low intake of both sodium and potassium had no effect on pressor sensitivity while a reduction of either ion alone depressed the pressor response. This might suggest that the ratio of sodium to potassium in the diet and in the body is of more importance in maintenance of vascular reactivity than is the absolute content of these ions.

Summary. The effect on the resting arterial blood pressure and on the pressor responsiveness to angiotensin has been investigated in rats maintained on diets of varying sodium and potassium content. A high sodium diet for 8 weeks did not affect resting blood pressure, but it induced a significant increase in the pressor response to angiotensin. Conversely, a low sodium diet reduced pressor sensitivity to angiotensin. A potassium deficient diet lowered blood pressure and the response to angiotensin. A high potassium diet produced no changes in these indices. Simultaneous deficiency of both sodium and potassium exerted no effect on blood pressure or the response to angiotensin.

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Received March 22, 1965. P.S.E.B.M., 1965, v120.