

INFLUENCE OF DIETARY POTASSIUM AND SODIUM/POTASSIUM
MOLAR RATIOS ON THE DEVELOPMENT
OF SALT HYPERTENSION*

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The reciprocal functions of sodium and potassium, fundamental to many biological phenomena, have long intrigued students of hypertension. As early as 1928, Addison (1) reported that potassium administration could lower elevated blood pressure in man and postulated that the hypertension prevalent in North America was due to low potassium diets and excess added salt (NaCl) consumption. Priddle made somewhat similar observations in 1931 (2). McQuarrie et al. (3, 4) reported that among some diabetic children who developed hypertension due to large quantities of salt, potassium chloride ingestion antagonized this effect of the NaCl. This reciprocity of sodium and potassium was further supported by the demonstrated usefulness of Kempner's rice-fruit diet in the therapy of hypertension (5, 6). The low sodium content of this diet is widely recognized but its high potassium content is perhaps not appreciated (7). This diet contains 20 times as much potassium as sodium. These findings make it at least conceivable that potassium mitigates the noxious effects of sodium on blood pressure in man. Experimentally, Meneely et al. (8, 9) found that KCl administration significantly enhanced survival of NaCl-poisoned rats and that, in some circumstances, it also moderated blood pressure.

In the work described here, we attempted to separate the effects of the absolute amounts of sodium and potassium in the diet from the effects of their molar ratios. For this we used a unique strain of rats, originally selected and bred for susceptibility to salt hypertension (10, 11) but subsequently found to be generally hyperresponsive to a number of the noxious stimuli commonly used to induce experimental hypertension (12-14). Our results are in accordance with McQuarrie's statement in 1950: "We believe . . . that the role of potassium as well as that of sodium must be taken into account in studies relating to the effects of electrolytes on the arterial pressure" (15).

Materials and Methods

Details on animal care, diet, and blood pressure (BP)¹ measurement have been published (16-18); therefore, only pertinent items are included here.

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¹ Abbreviation used in this paper: BP, blood pressure.

Animals.—The rats were derived originally from a single Sprague-Dawley strain. By selective inbreeding, two lines were evolved in this laboratory on the basis of their response to NaCl: the members of one strain (the sensitive or S strain) rapidly and predictably develop fulminating hypertension from the same high NaCl intake to which members of the other strain (the resistant or R strain) respond only mildly if at all. The same genetic determinants appeared to be operating when other techniques were used to induce experimental hypertension: deoxycorticosterone acetate plus NaCl; unilateral renal artery compression without NaCl; cortisone without NaCl; adrenal regeneration with NaCl; and uninephrectomy without (and, from some unpublished observations, with) NaCl (10–14). Experiments with these techniques indicated that the genetic substratum was a critical factor in whether or not experimental hypertension developed after a number of stimuli commonly thought to “cause” hypertension (13). In the studies reported here, only rats from the hypertension-prone (S) strain were used.

Diets.—The “basic diet” prepared in our laboratory, a modification of Nutritional Biochemicals Corporation’s (Cleveland, Ohio) “sodium-deficient test diet,” is as follows:

	% (w/w)
Sucrose	72
Vitamin-free casein	18
Butterfat (salt free)	5
Modified salt mixture P-H (dipotassium phosphate and sodium chloride omitted and replaced by equal weights of sucrose)	5
	100

The diet was supplemented with Vitamin Diet Fortification Mixture® (Nutritional Biochemicals Corporation).

The experimental diets were made by adding various amounts of NaCl, KCl, and Alphacel® to the basic diet. Alphacel®, a nonnutritive, nonelectrolyte “filler,” was used to make the cal/g value the same for all the diets. The diets are referred to below in terms of Na/K ratio; Na/K10, for instance, is the diet with a molar ratio of sodium to potassium of 10. The Na and K concentrations shown for the diets were checked by flame photometry. The bulk of the food was stored at -20°C until used, a 3 day supply being kept at room temperature.

Experimental Treatment.—For each experiment, 90 male weanling S rats were divided into 6 groups of 15 by assigning siblings systematically among each of the groups. Each group received only one of six experimental diets. Food and water were allowed *ad libitum*. Blood pressures and weights were measured at least every month for the duration of the experiment unless death or terminal illness supervened.

Analysis of Data.—Statistical comparison of means was made by chi-square, and analysis of variance was done with a special computer program.² Only *P* values ≤ 0.05 were considered significant; all *P* values < 0.01 were assigned this nominal value. The mean blood pressures for each group were based on cumulative final pressures, i.e., the pressure at the end of the experimental period or, if a rat died earlier, the least pressure while it was in “good health.” Good health was defined as maintenance of weight or a loss of no more than 10 g from any earlier maximum weight (19, 20).

Experiment I.—

Effect on BP of diets with constant absolute Na(Cl) concentration but different molar Na/K ratios: The 6 groups of 15 weanling S rats were fed different diets and observed for 12 months. (Through oversight weight and blood pressure measurements were not made for months 9

² We thank Keith Thompson for making the statistical analyses.

and 10 on groups consuming diet Nos. 4, 5, and 6.) The experimental diets, each containing 4.5% NaCl but having a different Na/K ratio, were as follows:

Diet No.	Basic diet	Alphacel®	NaCl	KCl	Total	Na/K ratio
	<i>g</i>	<i>g</i>	<i>g</i>	<i>g</i>	<i>g</i>	<i>molar</i>
1	89.76	5.17	4.50	0.57	100.0	10
2	"	4.59	"	1.15	"	5
3	"	4.31	"	1.43	"	4
4	"	3.83	"	1.91	"	3
5	"	2.87	"	2.87	"	2
6	"	0.00	"	5.74	"	1

RESULTS

The data on mean blood pressure are summarized in Table I and Fig. 1. On a constant NaCl intake (4.50%), the mean blood pressure response increased in stepwise fashion as the Na/K molar ratio increased, i.e., as dietary potassium decreased: Na/K10 > Na/K5,4,3 > Na/K2 > Na/K1 (all $P < 0.01$). As expected, the difference was greatest between the groups at the extremes of Na/K; at the end of the experiment, the group with Na/K1 had a mean systolic BP of 137.4 mm Hg as compared with 169.9 mm Hg for the group with Na/K10. The influence on mortality was less clear. In over-all mortality, only two pairs of groups differed significantly: Na/K2 < 4, ($P < 0.05$) and Na/K2 < 10 ($P < 0.01$). The monthly data, however, showed for month 11 a sharp difference between the lower and higher ratios: Na/K1,2 < Na/K4,5,10 ($P < 0.01$) and Na/K3 < Na/K4,5,10 ($P < 0.05$). These differences were muted by the low survival rates for all Na/K ratios in the 12th month. This experiment demonstrated that the molar Na/K ratio plays an important role in determining the hypertensinogenic capacity of sodium, and provided some evidence, although not unequivocal, suggesting that higher Na/K ratios are associated with higher mortality.

Experiment II.—

Effect on BP of diets with the same molar Na/K ratios but different absolute concentrations of NaCl and KCl: The 6 groups of 15 weanling S rats were fed different diets and observed for 6 months. Half of the groups received $\times 3$ the amount of NaCl (5.85 vs. 1.95%) that the other half received. KCl was added so that three different Na/K ratios resulted: Na/K = 1, 3, and 15. This allowed evaluation of diets with identical Na/K ratios but different absolute amounts of Na(Cl) and K(Cl). The diets were as follows:

Diet No.	Basic diet	Alphacel®	NaCl	KCl	Total	Na/K ratio
	<i>g</i>	<i>g</i>	<i>g</i>	<i>g</i>	<i>g</i>	<i>molar</i>
1	86.65	0.00	5.85	7.50	100.0	1
2	"	5.00	"	2.50	"	3
3	"	7.00	"	0.50	"	15
4	"	8.90	1.95	2.50	"	1
5	"	10.56	"	0.84	"	3
6	"	11.23	"	0.17	"	15

TABLE I
Effect on BP of Different Dietary Na/K Molar Ratios with Constant (4.50%) NaCl Concentrations

Months on diet	Na/K1			Na/K2			Na/K3			Na/K4			Na/K5			Na/K10		
	BP (mm Hg)		<i>f</i>															
	\bar{x}	SE		\bar{x}	SE		\bar{x}	SE		\bar{x}	SE		\bar{x}	SE		\bar{x}	SE	
1	108.3	3.09	1.00	109.8	3.17	1.00	119.3	3.11	1.00	115.2	3.28	1.00	109.1	4.02	1.00	116.1	3.66	1.00
2	124.9	3.05	"	123.3	2.64	"	126.2	2.64	"	118.6	2.07	"	118.4	1.93	"	130.7	2.42	"
3	119.8	2.39	0.93	121.2	2.51	"	125.1	3.29	"	133.7	3.28	"	131.3	3.33	"	148.9	5.01	"
4	126.0	2.27	0.87	130.5	3.24	"	132.1	3.53	"	133.2	3.03	"	126.9	2.84	"	146.7	3.91	"
5	123.3	1.65	"	128.2	4.60	"	136.6	4.14	"	134.3	4.15	"	141.5	3.83	"	163.6	3.01	"
6	125.1	2.41	"	134.9	5.03	"	142.6	5.69	0.93	140.3	4.76	0.93	145.1	5.15	0.93	166.0	3.98	"
7	125.0	2.78	"	134.7	5.45	0.87	146.9	3.80	"	144.5	3.80	"	152.9	4.20	0.87	165.3	3.48	0.80
8	132.5	3.77	0.73	147.0	4.17	0.80	153.6	3.77	0.73	149.0	4.28	0.80	159.9	4.42	"	164.4	3.45	0.60
9	No BP data	"	0.67	No BP data	"	0.67	No BP data	"	0.47	156.7	4.92	0.67	160.1	4.54	0.73	168.1	2.87	0.53
10	"	"	"	"	"	"	"	"	"	"	"	"	"	"	"	"	"	"
11	135.3	4.22	"	147.3	4.36	"	157.3	3.89	"	161.1	5.05	0.40	166.5	5.82	0.67	167.9	3.89	0.40
12	137.4	4.23	0.27	151.9	3.55	0.33	160.2	4.96	0.20	160.4	4.40	0.13	164.9	5.82	0.13	169.9	3.25	0.07
Mean BP for 12 months	126.9	1.06		135.2	1.47		142.3	1.49		142.4	1.62		145.1	1.89		156.5	1.60	

Fifteen rats in each group at beginning of experiment; *f* = fraction surviving.

Statistics among Na/K: (a) Blood pressure $10 > 5, 4, 3 > 2 > 1$ ($P < 0.01$); $3 = 4 = 5$; (b) Mortality: $2 < 4$ ($P < 0.05$); $2 < 10$ ($P < 0.01$).

RESULTS

The data are summarized for each group, except those on diet No. 6, in Table II and Fig. 2. Of the 15 rats on diet No. 6 (1.95% NaCl, 0.17% KCl, Na/K15), 12 died between 18 and 28 days (median 20) after going on the diet, before any BP data were obtained. One of the three survivors died during the 4th month with a BP of 186 mm Hg recorded at 3 months; a second lived 6 months but lost weight after the 4th month, at which time the BP was 122 mm Hg; the third survived the experiment and had a BP of 174 mm Hg at the

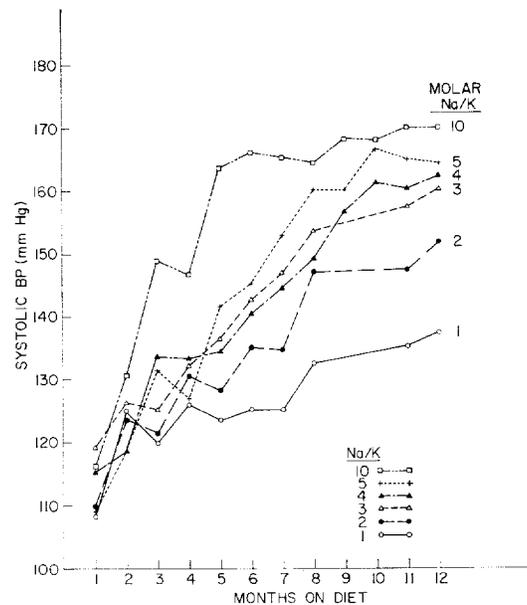


FIG. 1. Effect of BP on different dietary Na/K molar ratios in hypertension-prone rats. All six diets had 4.50% NaCl but each differed in KCl concentration.

end of 6 months. Because of these inadequate observations, this group is not considered further here.

On diets with the same Na/K ratios, the blood pressure response appeared to be determined by the NaCl intake; among the animals on either Na/K1 and Na/K3, the group on the higher (5.85%) NaCl intake also had the higher blood pressures ($P < 0.01$). No such comparison was possible for the Na/K15 groups because of the death of most of the rats in one group. As in experiment I, among animals on the same NaCl intake, average blood pressures generally were higher in groups on diets with a higher Na/K ratio, i.e., with lower potassium intake. However, with the NaCl concentrations used in this study, a diet with an absolute concentration of 5.85% NaCl but an Na/K ratio of only 1 was more hypertensinogenic than a diet with 1.95% NaCl but an Na/K

TABLE II
Effect on BP of Three Different Dietary Na/K Molar Ratios, Each with Two Different NaCl Concentrations

Months on diet	Na/K1			Na/K3			Na/K15								
	1.95% NaCl (diet 4)			1.95% NaCl (diet 5)			5.85% NaCl (diet 2)			5.85% NaCl (diet 3)					
	\bar{x}	SE	f												
1	126.3	2.88	1.00	131.8	2.33	1.00	129.9	3.13	1.00	128.6	2.69	1.00	151.0	5.29	1.00
2	138.2	2.77	"	157.5	2.54	"	142.0	2.90	"	155.9	6.14	"	191.7	8.02	0.87
3	143.5	2.84	"	160.3	4.03	"	147.6	2.68	"	169.8	5.73	0.93	208.4	6.89	0.53
4	128.3	2.38	"	153.6	5.70	0.87	139.0	4.09	"	167.7	6.50	"	201.8	6.83	0.40
5	135.6	2.41	0.93	159.0	6.77	0.73	151.1	3.12	0.87	164.6	5.68	0.53	199.9	7.24	0.27
6	140.5	3.52	0.60	162.2	6.97	0.40	158.6	4.17	"	170.7	5.45	"	203.3	6.33	0.13
Mean BP for 6 months	135.4	1.30		154.1	2.29		144.7	1.66		159.5	2.68		192.7	3.39	

Fifteen rats in each group at beginning of experiment; f = fraction surviving. No data on group with highest Na/K ratio (15) and lowest NaCl concentration because 12 died before end of first month.

of 3 ($P < 0.01$). When the absolute amounts of dietary KCl were the same (2.50% in diet Nos. 2 and 4), the group on the higher NaCl intake had the higher average blood pressure ($P < 0.01$).

The influence of added potassium on mortality was difficult to separate from the influence of blood pressure on mortality. In general, groups with the higher average pressures also suffered the higher mortality.

From experiment II it was concluded that sodium is hypertensinogenic; potassium is antihypertensinogenic; and at equivalent molar ratios, of the two effects, that of sodium is dominant.

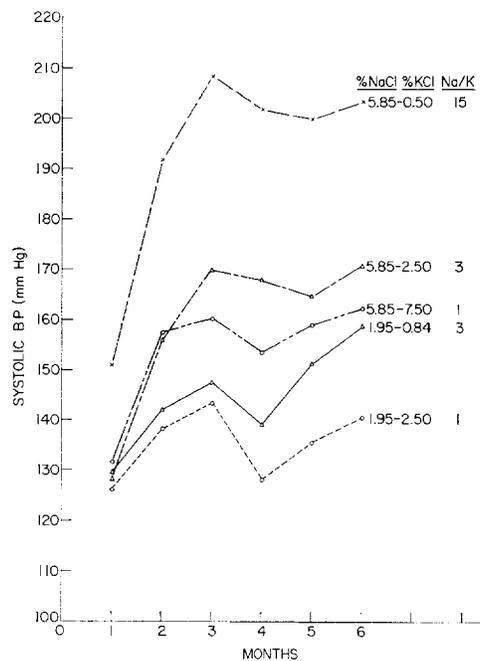


FIG. 2. Effect on BP of NaCl, KCl, and Na/K (molar) ratio. Results after 6 months. S rats only.

DISCUSSION

This work confirms that it is an oversimplification to speak of the hypertensinogenic effect of dietary sodium without consideration of dietary potassium. In these hypertension-prone rats increments or decrements of potassium chloride markedly decreased or increased, respectively, the hypertensinogenic influence of identical NaCl intakes. The dietary molar Na/K ratio emerged as an important determinant not only for the severity of salt hypertension but for whether or not hypertension developed at all. Sodium intakes that were only mildly hypertensinogenic with a high potassium intake were deleterious,

indeed, with a decreased potassium content. In groups of animals with sodium intakes differing by more than a factor of two (1.95 vs. 4.50% NaCl), groups on lower intakes could have equal or even higher blood pressures, depending on the respective potassium intakes. The group in experiment II (Table II) on 1.95% NaCl with an Na/K ratio of 3, for instance, had significantly higher ($P < 0.01$) pressures at 6 months (158.6 mm Hg) than did the group in experiment I (Table I) on 4.50% NaCl with an Na/K ratio of 1 (125.1 mm Hg). The data summarized in Figs. 1 and 2 allow these and other comparisons to be made.

Our work differed in several respects from that of Meneely et al. (8, 9) but the conclusion was essentially similar: potassium moderates the hypertensinogenic effect of sodium. Their long-term study was carefully controlled and involved large numbers of rats. They observed an ameliorating influence of added potassium on blood pressure only at high levels of NaCl ingestion (8.4 and 9.8%) whereas amelioration became clearly evident in our study at lesser NaCl intakes (1.95, 4.50, and 5.85%). They induced a striking improvement in survival with high potassium intake which was less evident here. Neither of these differences is substantive. All the rats in our study were from a strain genetically predisposed to develop hypertension with unusual sensitivity to the hypertensinogenic effects of NaCl. We developed this strain to obtain experimental animals with increased sensitivity to factors affecting blood pressure, but we may have simultaneously decreased the capacity to survive its effects. While we could observe the moderating effects of KCl on the hypertension that readily developed, the rapid progression of the hypertension may have blurred the enhanced survival observed in Meneely's study with rats much less sensitive to salt.

Most investigations of the interactions of sodium and potassium have dealt with the toxic effect of sodium in potassium deficiency induced in various ways (21-30). Their results make it seem likely that the high mortality of the animals on diet No. 6 in experiment II was due primarily to an inadequate K intake. The potassium requirement of young rats is about 0.15-0.18% K in the diet (31), roughly twice that in diet No. 6. A given Na/K ratio is most toxic when high levels of Na are fed with low levels of K (23). The 1.95% NaCl in diet No. 6 would result in Na intakes approximating 15 times the minimum requirements for growth (31); this concentration is about twice that in most commercial chows. Diet No. 6 may therefore be considered high in Na and frankly deficient in K.

In contrast to our work and to that of Meneely et al., a series of papers by Friedman, Freed, and Rosenman (25-30 and others) suggests that potassium restriction has a depressor effect on blood pressure and that the addition of excess sodium enhances this depressor effect. One clinical study (32) was compatible with this interpretation. This concept is now part of the literature on hypertension although, in our opinion, its long-term effect has been to becloud

rather than clarify the respective roles of sodium and potassium in hypertension. Friedman et al. made uniformly short-term observations, commonly after the rats had been on an almost potassium-free diet (0.006% K) for 6–8 wk. In view of the well-established K requirements, such a diet is not compatible with normal growth or even life. The authors mention in most of these papers that the rats suffered from debilitation. Deriving vital conclusions from studies on such animals seems hazardous, indeed. We would predict that gross deficiency of any essential nutrient will ultimately be associated with a decline in blood pressure as debility increases. We have observed a similar phenomenon, for example, in rats after 4 or 5 wk on a grossly Na-deficient diet (33). In our own experience (unpublished) diets containing only 0.006% K were so debilitating as to nullify their use as physiological tools; for instance among 20 animals from the S strain kept on this K-deficient regimen for a maximum of 2 wk, 9 died before or shortly after the diet was replaced by normal chow, and among 24 maintained for a maximum of 4 wk, 21 died similarly. Friedman et al. reported (25, 26) that in some cases the addition of sodium to the K-deficient diet was followed by a further fall in blood pressure. This is not surprising in view of the clear-cut evidence that added NaCl is highly toxic and rapidly lethal to K-deprived rats (21, 23–26, 34).

The mechanism by which potassium moderates hypertension is unclear. Others (35) have found that the spontaneously hypertensive rat (36) was protected by dietary KCl against the hypertensive effect of a high salt diet. Although the KCl prevented the rise in exchangeable sodium associated with their high-salt diet, the “high body sodium” theory does not hold for our rats since we do not find an increase in total body sodium, as measured by either isotopic exchange or carcass analysis (37).

Chronic potassium loading is a potent stimulus to aldosterone production in a number of mammals, including the rat (38). Enhanced aldosterone production, however, in association with the high NaCl intakes used here should be expected to promote hypertension, rather than to moderate it as found in our study. A change in plasma renin activity is a possibility, but Boyd et al. (38) did not observe a change after oral potassium loading in rats; Veyrat et al. (39) as well as others have reported suppression of plasma renin activity by oral potassium loading in sodium-restricted normal humans. Our genetically hypertension-prone rats were not on restricted sodium intakes but, rather, excess sodium intakes. In addition, these rats normally have plasma renin activities that are suppressed even before the development of hypertension and further decreased by NaCl and the development of hypertension.³ Reid and Laragh (34) found that the increased pressor response to angiotensin observed in rats maintained on a high-sodium diet did not occur among animals

³ Iwai, J., K. D. Knudsen, and L. K. Dahl. Longitudinal study of renin activity levels in hypertension-resistant and hypertension-prone rats during the development of salt and renal hypertension. Manuscript in preparation.

receiving either NaCl plus KCl or a high potassium diet alone. This moderation of the pressor response to angiotensin by potassium might play a role in our experiments.

Of all the possibilities, the most appealing to us is that added potassium modifies smooth muscle activity in arterioles, the major resistance vessels. Many reports suggest that in hypertension there may be an increase in arteriolar wall sodium. This increase was originally seen by Tobian and Binion in rat aorta (40) and Tobian's group has found it in arterioles also (41). We have long been intrigued by the possibility that one of the genetic defects leading to hypertension might be associated with a fault in the transduction of energy in the arterioles. Whether Na-K exchange is coupled is questionable but there is little doubt that smooth muscle contraction is associated with an influx of Na and an efflux of K; during relaxation these ions move in the opposite direction and, at least in the case of Na, require energy for transportation against the considerable electrochemical gradient between the relatively low intracellular, and the high extracellular, Na concentrations (42). The extrusion of Na and uptake of K appear to be mediated by a system having the properties of a Na,K-dependent adenosine triphosphatase (42). This energy system has a high dependency on potassium (43).

SUMMARY AND CONCLUSION

Among genetically hypertension-prone rats, dietary sodium (chloride) was demonstrably hypertensinogenic and potassium (chloride) antihypertensinogenic.

On diets containing the same NaCl but different KCl concentrations, mean blood pressure was greater in rats receiving less dietary potassium, i.e., diets with a higher Na/K molar ratio.

On diets with different absolute concentrations of NaCl and KCl, but the same Na/K molar ratios, rats on the higher absolute NaCl intakes had the higher blood pressures.

On diets with different absolute concentrations of NaCl and KCl, and different Na/K molar ratios, a group on a lower absolute NaCl intake but with a higher Na/K ratio could have more hypertension than a group on a higher absolute NaCl intake but with a lower Na/K ratio.

At equivalent molar ratios, the respective effects of these two ions on blood pressure were dominated by that of sodium. It was concluded that the dietary Na/K molar ratio can be an important determinant for the severity, or even development, of salt-induced hypertension.

The mechanism of the moderating effect of potassium on sodium-induced hypertension was unclear.

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