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Strain Differences in the Predisposition to Dietary Salt-Induced Hypertension and to Preference for Sodium Chloride in Rats under Various States of Protein Nutrition

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ABSTRACT

The preference for NaCl and the relation between dietary salt and the susceptibility to hypertension were investigated using several strains of rats. One important fact often overlooked is that the tendency to develop hypertension has a strong genetic component. Sprague–Dawley (SD) rats, fed a chronic excess of sodium in the diet, showed increased systolic blood pressure in accordance with dietary NaCl concentration. Spontaneously hypertensive rats (SHR) developed and maintained hypertension whether on a low or high sodium diet.

In the experiments reported here, the effect of sodium intake on adult blood pressure levels and preference for salty taste was determined using three strains of rats: SD, SHR and Wistar/SLC (Wistar). Hypertension was not induced in the Wistar rats when they were supplied with dietary sodium levels of 2 and 4% even though the diets were introduced at either 21 days, 3 or 7 months of age and continued to the age of 2 years. The F_2 generations of Wistar rats, given 1% NaCl solution for 3 generations starting at 3 months of age to 4 months of age, remained normotensive. In liquid preference tests, the Wistar strain showed no preference for NaCl solution. In contrast, the SHR showed a strong preference for NaCl solution regardless of the dietary sodium level. The infant SHR, supplied with less than 0.05% dietary sodium (but equal to the minimum sodium requirement for the Wistar strain) failed to grow completely, indicating its requirement to be several times higher than normotensives.

SHR displayed a strong preference for NaCl, but Wistar rats did not. Preference for NaCl in SD rats was in between both. The total sodium intake in both normotensive and SHR declined as dietary protein was increased; the decrease was much greater in normotensive animals (SD rats), however a preference for monosodium L-glutamate (MSG; umami taste) was also observed in SHR, as well as in normotensive rats, when dietary protein was sufficient, but the preference for NaCl was sustained in SHR despite the fact that dietary NaCl intake decreased. The development of hypertension in SHR was essentially the same regardless of dietary protein content beyond the requirement for normal growth, but their state of hypertension was deteriorated by protein deficiency during growth, in association with the strong preference for NaCl. SHR was unable to grow well under a severely restricted sodium intake or to nurse pups under loading of NaCl plus equimolar KCl, presumably because of a genetically determined mineral metabolism dysfunction.

These facts suggest that taste preference is not fixed but closely dependent on the nutritional state and genetic factors. It is further suggested that a small portion of human population may fall into similar "responder" and/or "non-responder"-genetic categories.

INTRODUCTION

Epidemiological studies (Dahl and Love, 1954; Dahl, 1958, 1960a; Issacson et al., 1963; Freis, 1976; Page, 1976) suggest that the incidence of hypertension in different countries is dependent upon the level of dietary salt consumption. Particularly acute examples of this phenomenon exist in South America (Oliver et al., 1975), some Pacific islands (Maddocks, 1961, 1967; Prior et al., 1968; Page et al., 1974), and northern Japan (Dahl, 1960b; Sasaki, 1964; Hatano, 1974) (Fig. 1). In contrast, there is little incidence of hypertension in inhabitants of the oases of the Sahara, although they consume water high in sodium (Pauque, 1980). It has also been reported (Fallis et al., 1962; Wotman et al., 1967; Schechter et al., 1973; Thomas, 1973; Henkin, 1974; Schechter et al., 1974) that individuals with hypertension generally display elevated threshold or greater preference for salty taste than do normotensives. However, an important fact which is often overlooked is that the tendency to develop hypertension may have a strong

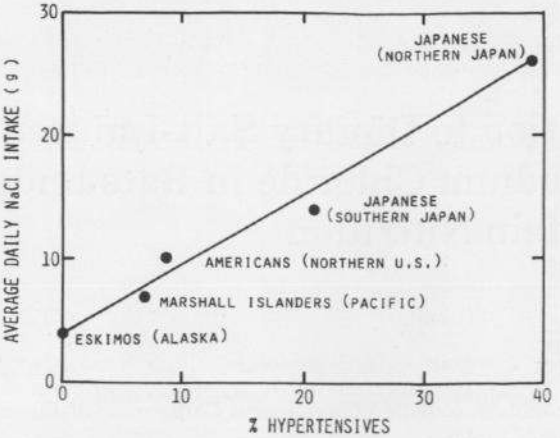


Fig. 1. Relation between the incidence of hypertensives and the average daily sodium chloride intake in people of different areas of the world.

genetic component (Zinner et al., 1971; Swaye et al., 1972; Thomas, 1973; Torii, 1980). The family of an individual with essential hypertension is likely to have a high incidence of this disease regardless of dietary salt intake levels.

RAT STRAINS AS MODELS OF HUMAN RESPONSE TO SALT

This chapter describes studies that investigate relationships among essential hypertension, the susceptibility to hypertension and dietary salt intake, the genetic predisposition to hypertension, the preference for salty taste, nursing on a hypertensive parent, and aging. We used three strains of rats to serve as models for postulated types in the human population (Ebihara and Martz, 1970, 1971; Ebihara, 1972). The first strain of rats used was the Sprague-Dawley (SD) in which chronic ingestion of excessive amounts of salt (NaCl) leads to the development of a pathological hypertensive process (Meneely et al., 1952, 1953; Dahl and Love, 1954, 1957; Tucker et al., 1957; Dahl, 1958; Meneely and Ball, 1958; Dahl, 1960a,b, 1961; Dahl et al., 1962; Dahl and Schackow, 1964; Dahl, 1968; Dahl et al., 1970, 1972). These SD rats developed an increase in systolic blood pressure in accordance with dietary NaCl content. The second strain of rats used was the spontaneously hypertensive rats (SHR). This strain was segregated from the Wistar strain (Wistar/Kyoto) in 1963. It is characterized by its ability to develop and maintain hypertension independent of NaCl intake (Okamoto and Aoki, 1963; Okamoto et al., 1966). The last strain used was the Wistar/SLC strain (Wistar) which displays little preference for salty taste, i.e., NaCl, and maintains normal blood pressure.

RESULTS AND DISCUSSION

Unlike the case of SD rats, hypertension resulting from dietary salt intake could not be induced in Wistar rats supplied with diets containing 0.28% (as control), 2%, or 4% (w/w) Na (0, 4.8% and 9.6% NaCl, w/w, added in basal diet, respectively). The diets were introduced either at 24 days, at 3 months, or at 7 months of age and continued to approximately 2 years of age. Systolic blood pressure and survival rate of each of the excessive sodium diet group were essentially the same as controls (Fig. 2), although body weight gain and weight maintenance levels were suppressed slightly in accordance with Na dilution of the diet.

In further studies, to determine the development of hypertension under an excessive intake of salt in semi-isotonic solution, Wistar rats were given either 0.17 M NaCl solution or deionized water (control) as the sole source of drinking water for three generations starting at 3 months of age for the parent to 4 months of age for the third generation (Table 1). The Wistar rat appears to tolerate excessive NaCl loading, maintaining normal sodium and water metabolism. This tolerance is in contrast to the SD rats which under similar conditions exhibit renal failure and edema (Meneely et al., 1952, 1953).

Louis et al. (1971) and Aoki et al. (1972) reported that the growth of the weanling SHR was suppressed under a severely restricted Na diet (0.03–0.10%), indicating a higher requirement of dietary Na in SHR than the minimal 0.05% Na in diet of normotensive albino rats. Therefore, an experiment to measure the growth of SHR placed on restricted Na diets from birth was conducted in order to estimate the minimal requirement of Na for normal growth and to examine the dietary effects on systolic blood pressure with age. Four groups were studied. Group A rats served as the control group. Group B rats comprised the Na-restricted group. The last two groups were nursed by either hypertensive (SHR) (Groups Cs) or normotensive (Wistar) (Group Cw) foster-dam immediately after birth (see Fig. 3). Dams of Group B, Cs and Cw were supplied with a 0.03% Na diet from birth until the pups were weaned at 21 days of age. This level is the minimal requirement of Na for lactation to take place in albino rats. The body weights of the SHR pups were similar to control at 21 days of age (weaning). Growth of weanling SHR (Group B) was severely depressed during Na restriction when the SHR dams were given a Na-restricted diet after delivery.

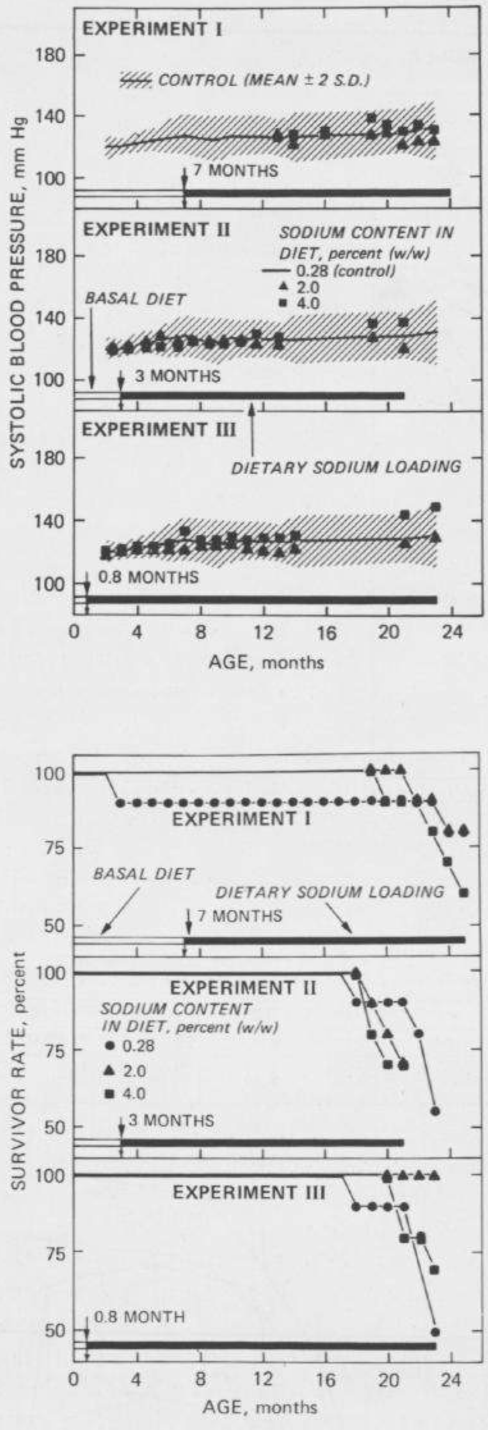


Fig. 2. Systolic blood pressure and survival rate in Wistar rats under chronic dietary salt loading. Wistar rats were supplied with diets containing 0.28% (as control), 2% or 4% (w/w) Na (0, 4.8% and 9.6% NaCl (w/w) added in basal diet, respectively). The diets were introduced from 24 days, 3 and 7 months of age and continued to approximately 2 years of age, noted at the bottom as thick solid line. Systolic blood pressure in individual animals was measured monthly by the tail-plethysmograph method without anesthesia and mean values in each group are displayed. Shaded area is the mean value of control group with two standard deviations.

TABLE 1

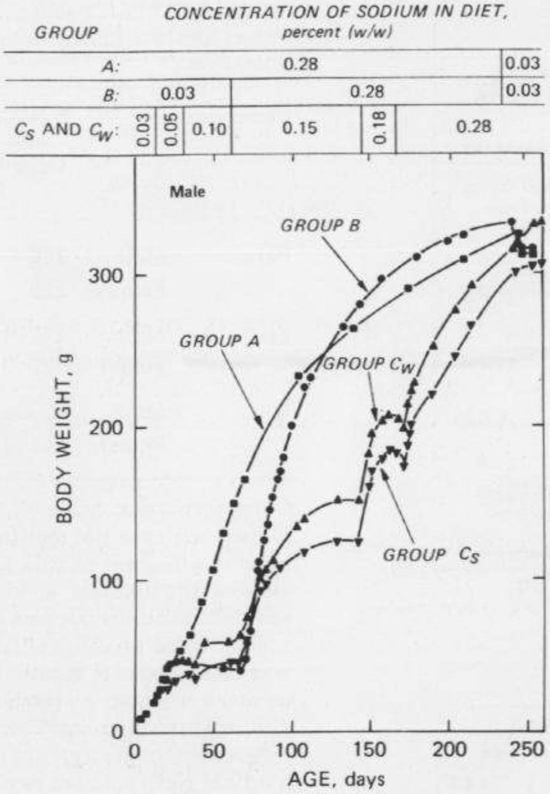
Effect of 0.17 NaCl solution (as the sole source of drinking water) for three generations on the systolic blood pressure of Wistar rats[a]

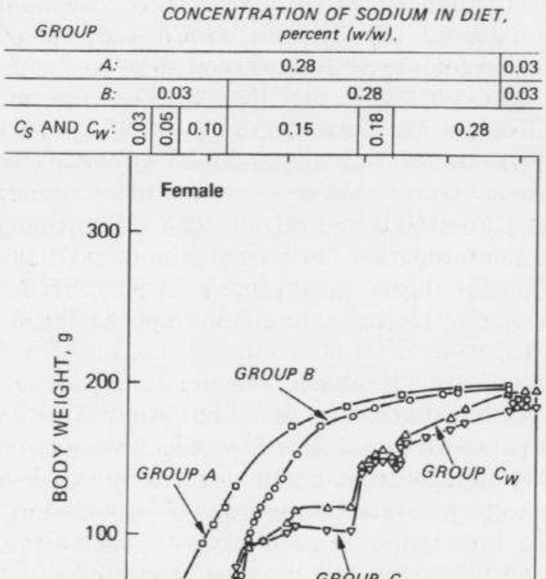
Generation	Sex	Systolic blood pressure (mm Hg)			
		Deionized water[a]		0.17 M NaCl solution[a]	
Parent	Male	126	(N = 1)	124	(N = 1)
	Female	120	(N = 1)	118	(N = 1)
F_1	Male	122±4	(N = 4)	122±3	(N = 4)
	Female	120±2	(N = 4)	118±4	(N = 4)
F_2	Male	123±6	(N = 19)	121±4	(N = 29)
	Female	121±4	(N = 20)	118±3	(N = 29)

[a]A pair of normotensive Wistar rats (parent) were supplied ad libitum with normal diet (a commercial chow). Two generations of offspring of this pair were used. The male which showed the highest level of systolic blood pressure was selected as the sire. He was bred with female litter mates. The systolic blood pressure of each individual at each generation was measured at 4 months of age. These data are expressed as mean or mean ± standard deviation. N = the number of animals in each group. There were no statistically significant differences between groups supplied with deionized water and a 0.17 M NaCl solution as drinking water.

Following weaning, animals of Groups Cs and Cw were supplied with diets of increasing Na content as they matured. The plateau level of body weight in male and female SHR increased step-wise with the increments of Na in diet (Fig. 3). The minimal Na requirement for normal growth of SHR was estimated to be 0.27% (male) and 0.23% (female). These values are close to the amounts found in commercial chow (0.26–0.31% in diet), but they are much higher than those reported for normal albino rats (0.05%).

Systolic blood pressure of these SHR was measured by the tail-microphone method (Fig. 3). Na restriction in SHR of Groups B, Cs, and Cw from birth onward suppressed the usual increase seen in systolic blood pressure noted for Group A with age. Animals of Group Cs and Cw, which were supplied with diets of increasing Na content up to a level of 0.28%, grew to a normal size, and displayed significantly lower systolic blood pressure than Group B. Furthermore, the systolic blood pressure of Group Cw was significantly lower than that of Group Cs. Introduction of a 0.03% Na diet (equal to minimal Na requirement for maintenance in albino rats) for 10 days to Group A and B during adulthood led to a significant decrease in systolic blood pressure of Group B, which had received restricted Na dietary


CONCENTRATION OF SODIUM IN DIET, percent (w/w)
GROUP
A: 0.28 0.03
B: 0.03 0.28 0.03
C_S AND C_W: 0.03 0.05 0.10 0.15 0.18 0.28
Male
GROUP B
GROUP A
GROUP C_W
GROUP C_S
BODY WEIGHT, g
AGE, days


CONCENTRATION OF SODIUM IN DIET, percent (w/w).
GROUP
A: 0.28 0.03
B: 0.03 0.28 0.03
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Female
GROUP B
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GROUP C_W
GROUP C_S
BODY WEIGHT, g
AGE, days

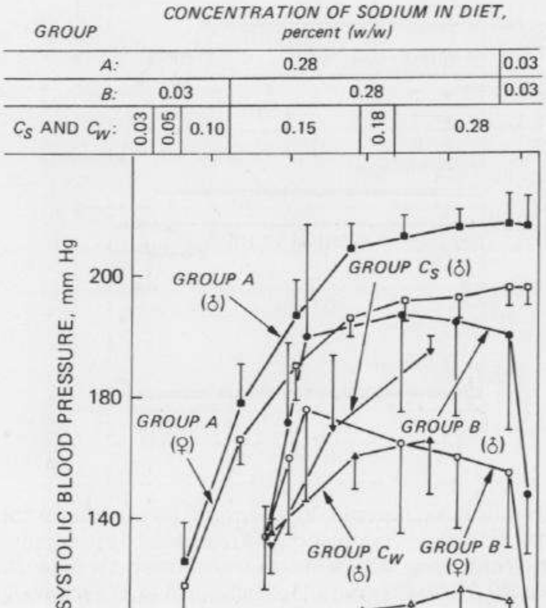
CONCENTRATION OF SODIUM IN DIET, percent (w/w)
GROUP
A: 0.28 0.03
B: 0.03 0.28 0.03
C_S AND C_W: 0.03 0.05 0.10 0.15 0.18 0.28
GROUP A (♂)
GROUP C_S (♂)
GROUP A (♀)
GROUP B (♂)
GROUP C_W (♂)
GROUP B (♀)
NORMOTENSIVE CONTROL (WISTAR RATS) (♂)
SYSTOLIC BLOOD PRESSURE, mm Hg
AGE, days

Fig. 3. (*Opposite page*). Pattern of growth and systolic blood pressure of weanling SHR under dietary Na restriction. Sib-mated male and female SHR (F_2 generation) were used. Animals of Group A (sqare boxes) (control) (N = 10), B (circles) (N = 11), Cs (inverted triangles) (N = 6), and Cw (triangles) (N = 6) were supplied ad libitum with deionized water as the sole source of drinking water and diets containing varying quantities of sodium. The exact amount of Na in the diet at any particular time for any particular group of animals can be found by referring to the display above the actual figure. Animals of Group Cs were nursed by a foster SHR (hypertensive) dam and Group Cw by a foster Wistar (normotensive) dam. Animals in Groups A and B were nursed by their own SHR mother. At 8 months of age, Groups A and B were provided with dietary Na restriction (0.03% Na diet) for 10 days, but the magnitude of body weight decreases in both groups was essentially the same. Body weight of Group Cw was significantly higher than that of Group Cs from weaning to the conclusion of the experiment. Systolic blood pressure in each group of SHR and male Wistar rats (N = 10) was measured by the tail-microphone method. In the case of female SHR, both groups Cs and Cw were omitted from the systolic blood pressure measurement.

levels during the neonatal period. Animals in Group A (control), that were not subjected to Na restriction during growth, did not respond to this dietary treatment as adults (Fig. 3). These findings were observed in both sexes. The results suggest that the neonatal period may be particularly important for SHR in developing adult systolic blood pressure.

SHR also displayed a strong preference for NaCl regardless of the amount of dietary salt intake. The preference for NaCl in aqueous solution in both SHR and Wistar rats under various levels of dietary salt intake was determined quantitatively (Torii et al., 1986). In liquid preference tests, the Wistar rats showed no preference for 0.17 M NaCl solution when they were fed diets containing 0.28, 2.0, or 4.0% Na (Fig. 4). On a diet containing 0.03% Na, a small preference for NaCl solution was observed, reflecting

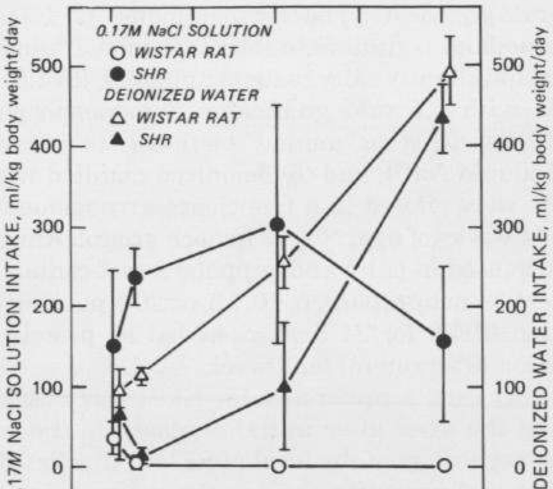

Fig. 4. Preference for sodium chloride solution in SHR and Wistar rats supplied with a diet containing varied amounts of sodium. Both strains of rats were allowed access to 0.17 M NaCl solution and deionized water as drinking water. Basal diet was formulated as free of sodium as possible (0.03% Na in diet). Each experimental diet (0.03, 0.28, 2.0, or 4.0% Na in diet) was prepared by addition of an appropriate amount of NaCl to the basal diet.

the amount required for physiological needs.

Unlike the Wistar rats, the SHR showed a strong preference for 0.17 M NaCl solution across a dietary Na level from 0.03 to 4%, and displayed a maximal preference for NaCl in solution at 145 mEq/l, a value equal to the plasma Na concentrations (Fig. 4).

While monitoring the growth of neonatal SHR or Wistar rats, lactating dams of both strains were given water, NaCl (0.17 M) or a NaCl (0.17 M) plus KCl (0.17 M) equivolume mixture as the sole source of drinking water. The Wistar and SHR dams were tested for preference for these solutions versus deionized water in a three-bottle test.

Normal SHR dams, 5 months of age, showed a strong preference for the NaCl solution but not for NaCl plus KCl (Fig. 5). After removal of the NaCl solution from individual cages, SHR dams preferred deionized water as a drinking solution when tested against NaCl plus KCl. A Wistar dam given 0.17 M NaCl solution as drinking water from birth to 80 days of age (at 5 months of age) also preferred a 0.17 M NaCl solution but did not prefer 0.17 M NaCl plus equimolar KCl solution (Fig. 5). Potassium ion in SHR might effect maintainance of Na retention in the body. Even though Na intake together with K suppressed the blood pressure increase in the SD rat (Meneely and Ball, 1958; Dahl et al., 1972), the same treatment was not clearly effective in the SHR. It is also interesting that salt preference is "imprintable" even if the subject is a normotensive Wistar rat (Torii, 1980).

Next, SD rats which respond to excessive salt intake by increased systolic blood pressure, were used to investigate the relationship between susceptibility to hypertension and treatments begun at the neonatal age. Male SD rats of an F_2 generation (N = 42) derived from a normotensive pair were separated into seven groups. SD rats that were fed a normal diet ad libitum were injected once with either isotonic or hypertonic saline (300 and 600 mOsm/kg H_2O, respectively) intraperitoneally (1.25 g NaCl/kg body weight) at 10, 20, and 30 days of age. At 6 and 12 months of age, the systolic blood pressure was observed to be significantly increased for those SD

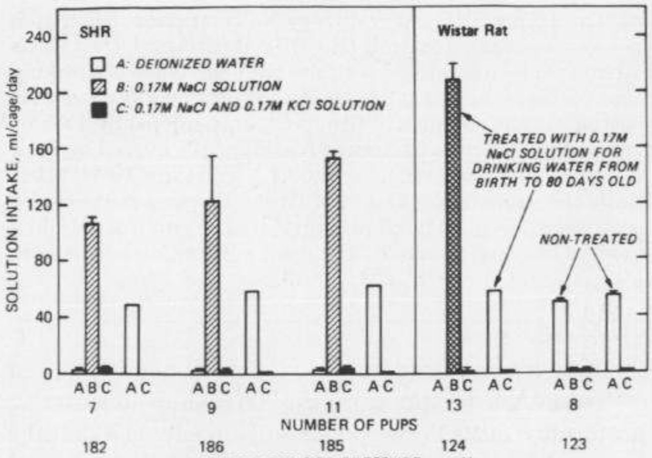

Fig. 5. Preference for NaCl alone or with KCl solutions in SHR and Wistar dams during lactation. Intake of deionized water (A), 0.17 M NaCl (B), and 0.17 M NaCl plus equimolar KCl (C) solution was determined for SHR and Wistar dams, 5 months of age. The pups remained in the cage with the mothers. From day 2 after delivery to day 4 intakes of solutions A, B, and C were recorded. On day 5, only solutions A and C were offered. A Wistar dam, 5 months of age, given 0.17 M NaCl solution as the sole source of drinking water from birth to 80 days was given a choice, using the same time paradigm as the SHR, among solutions A, B, and C, then between A and C. These data are compared with a control ("nontreated") animal given deionized water as a fluid source from birth to 80 days. After the preference tests, systolic blood pressure and number of pups were determined (day 7). Column sets showing comparisons among A, B, and C are expressed as intake per cage per 24 h and include one standard deviation.

rats injected with either the isotonic or hypertonic saline on days 20 or 30, but no change in blood pressure was observed for those animals injected when they were 10 days of age.

This observation led to the following hypotheses: (a) the Wistar rat is a "non-responder" to excessive dietary Na intake from weaning and during life. Yet this strain is "imprintable" for salt preference if given 0.17 M NaCl solution during its early growth stage; yet it does not develop high blood pressure; (b) the SD rat is a "responder" either to excessive dietary Na loading or to treatment at neonatal age, and will develop high blood pressure as an adult; (c) the SHR is an "inherited nonresponder" to restricted or excessive dietary Na treatment. Under all conditions of dietary Na, it will develop hypertension. Moreover, SHR is unable to grow under a severely restricted Na intake (equal to minimal Na requirement for growth and maintenance in normotensive albino rats); (d) the SHR that consumed a low Na regimen during growth is able to respond to a low Na diet at adult age, resulting in the decrease of systolic blood pressure compared with other SHR not subjected to this diet. In addition, the minimal Na requirement for normal growth and the incremental change of systolic blood pressure with age could be lowered if the SHR pups were nursed by a normotensive Wistar female.

Consequently, when extrapolating these findings to the human situation, it may be hypothesized that the human population contains individuals of at least three types: (1) those who will not develop hypertension regardless of dietary salt intake, (2) those who are unable to grow normally under "low" salt diets and will develop hypertension with or without high salt intake over their requirement for growth, and (3) those who have a genetic predisposition to high salt intake and who will, as a consequence of diet, develop this disease. It may be possible to treat the last type by a diet programmed to lower salt intake. The most important problem is how to confirm and classify these different types of people with or without the predisposition to hypertension before that portion of the human population becomes hypertensive.

The preference for salty taste seems to be an important factor in classifying strains of rats as to the likely development of high blood pressure. Therefore, additional experiments were conducted to examine the preference for salt in SD rats and SHR under various levels of protein restriction (Torii et al., 1986, 1987). Five taste solutions were used: (1) 500 mM glycine (Gly) (sweet to humans), (2) 150 mM monosodium L-glutamate (MSG) (a mixed "umami" taste and slightly salty taste to humans), (3) 4.5 mM MSG with 4.5 mM guanosine 5′-monophosphate (GMP) (eliciting an "umami" taste only to humans), (4) 150 mM NaCl, and (5) deionized distilled water. These were offered in a five-choice arrangement to rats (4 weeks of age, N = 13 in each group). Animals were housed in pairs and supplied a diet containing either 0% (nonprotein), 5, 10, 15, or 20% purified egg protein (PEP) for 34 days preceded by protein restriction (0% protein) for 1 week.

In SD rats, a preference for NaCl was observed during the week after initial exposure to the solutions, regardless of the level of PEP in the diet (Fig. 6). The preference for NaCl in the group of rats fed the 0% and 5% PEP diet was sustained and their growth was severely suppressed during the experiment. On the other hand, NaCl intake declined concomitantly with an increase in intake of both MSG-containing ("umami") solutions (i.e., solution Nos. 2 and 3) when 10, 15, and 20% PEP diets were offered to rats. These rats also grew normally. Moderate Gly intake was observed only at the onset of exposure to these stimuli regardless of experimental diets offered. Preference for Gly may be indicative of its

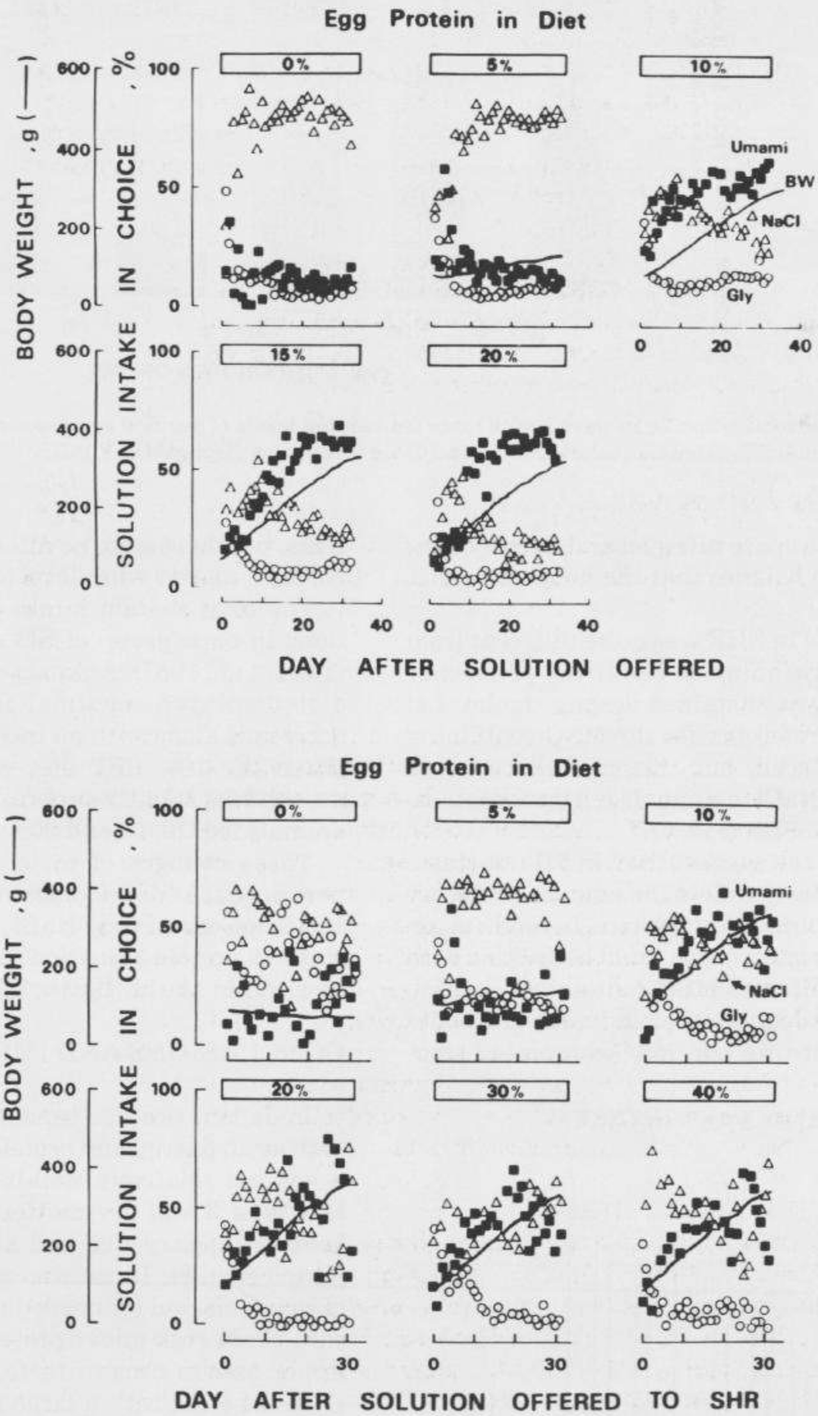

Fig. 6. Pattern of preference for NaCl, glycine (Gly), and MSG-containing ("unami") taste stimuli in weanling rats fed different levels of protein. Male SD rats (left) and SHRs (right) (4 weeks of age, N = 13/group except for the nonprotein diet group where N = 6) were supplied with a diet containing purified egg protein (PEP) at 0, 5, 10, 15, or 20% PEP for 34 days. This feeding period was preceded by a 7 day period during which all animals were fed a 0% protein diet. Five taste solutions were offered in a multi-choice arrangement: (1) 500 mM Gly, (2) 150 mM MSG, (3) 4.5 mM MSG with 4.5 mM GMP, (4) 150 mM NaCl, and (5) water. The figure displays the percentage intake based on the total volume intake of Gly (hollow circles), NaCl (hollow triangles), and both solutions containing MSG (i.e. 2+3) (filled square boxes). Water intake was negligibly small and is not noted on the figure. Mean body weight appears as a solid curve.

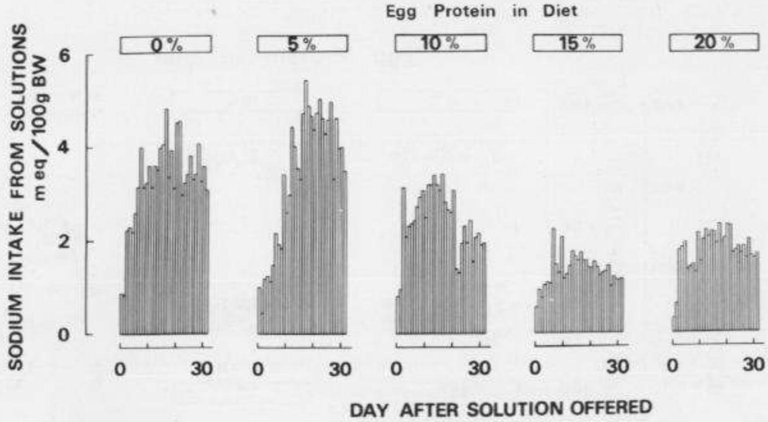

Fig. 7. Pattern of total sodium intake in weanling SD rats fed varying levels of purified egg protein (PEP). Sodium intake was calculated from all sodium ingested (i.e. solutions 2, 3, and 4) via solution as displayed in Fig. 5.

presumed ability to spare nitrogen and thereby minimize the negative balance that the nonprotein diet induces.

Taste preference in SHR was quite different from that in normotensive animals. The strong preference for NaCl in SHR was sustained despite the level of PEP in the diet. Preference for the MSG-containing solutions was induced, but this preference never overcame that for NaCl in animals fed diets containing more than 10% PEP (Fig. 6).

These observations suggest that, in SD rats, taste preference may closely reflect the amount of dietary protein, and that intake of protein beyond its required level for normal growth could be coupled with a preference for salt- and MSG-containing taste solutions. In SHRs, adequate protein intake also could elicit the preference for the MSG-containing solutions, but there were no alterations in preference for NaCl no matter what level of PEP was offered.

The total sodium intake from all drinking solutions in each group of SD rats is shown in Fig. 7 (Torii et al., 1987). Animals eating the 0 and 5% PEP diet displayed maximal intake. Sodium intake decreased along with an increase in PEP in the diet. When the 10% PEP diet was offered to the rats, growth was slightly suppressed compared to that of animals fed the 15 and 20% PEP (Fig. 6).

These changes of taste preference lead one to postulate that development of a preference for taste solutions containing NaCl may be related to the state of protein nutrition (Torii et al., 1986, 1987; Mori et al., 1991a, 1991b; Tabuchi et al., 1991).

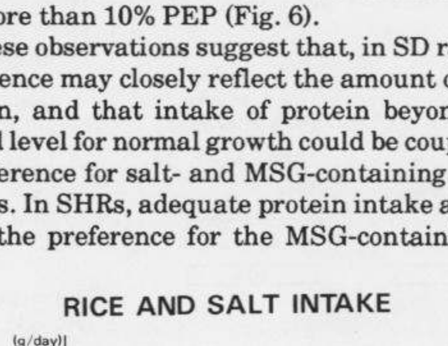

Fig. 8. Relation between rice and salt intake in Japan. Daily rice and salt intake values were obtained from the national survey of nutrition in 1986. Values are expressed as the mean daily salt intake in each group. The range of rice consumed per group is noted at the bottom of the figure.

CONCLUSIONS AND IMPLICATIONS

In Japan, rice has been the most important food both as an energy and protein source. Yet it contains a low but relatively well-balanced protein level of less than 3% of dry matter. A positive correlation between dietary rice and salt intake has been reported (Fig. 8). Those who consume a large amount of rice preferred (or needed to eat) a large amount of salt. Since rats under protein restricted conditions prefer salt to umami taste, the salt preference of those who eat both a large amount of rice and salt may be related to their protein nutrition. Indeed, as the composition of dietary protein intake has increased in Japan year by year, dietary salt intake has decreased (Figs. 9 and 10). These facts suggest that the salt preference in some people may be related with protein nutrition, like it is for some strains of rats, such as SD rats. These strains can be made hypertensive by feeding high salt diets, and they show a preference for salty taste. Therefore, it

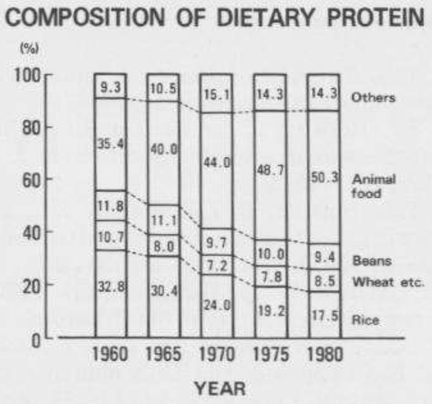

Fig. 9. Change of dietary protein sources in Japan, from 1960 to 1980. Composition of dietary protein was determined from the national survey of nutrition across two decades averaged every five years. Grain crops were categorized as rice and all others (wheat, etc.).

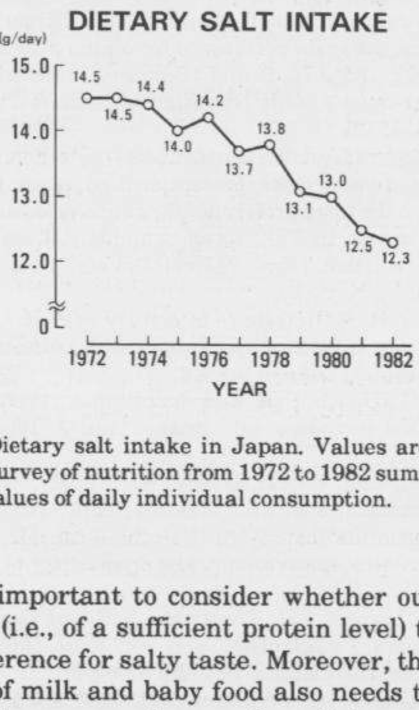

Fig. 10. Dietary salt intake in Japan. Values are from the national survey of nutrition from 1972 to 1982 summarized as average values of daily individual consumption.

may be important to consider whether our food is suitable (i.e., of a sufficient protein level) to control our preference for salty taste. Moreover, the protein quality of milk and baby food also needs to be considered, because preference for salt is possibly imprinted. The preference for salty solutions is also dependent on Ca intake, as has been recently shown by Tordoff et al.. The lower the Ca intake, the higher the appetite for salt. Those who have no family history of adult hypertension need not be concerned about moderate salt intake. Those who have a family history of hypertension may wish to moderate their salt intake. It is possible that these individuals may be able to change their preference for salt (Bertino et al., 1982). It would be useful to find a predictive marker of responders and non-responders to dietary-induced hypertension.

REFERENCES

Aoki, K., Yamori, Y., Ooshima, A. and Okamoto, K., 1972. Effects of high or low sodium intake in spontaneously hypertensive rats. Jpn. Circ. J., 36: 539–545.

Bertino, M., Beauchamp, G.K. and Engelman, K., 1982. Long-term Reduction in Dietary Sodium Alters the Taste of Salt. Am. J. Clin. Nutr., 34: 1134–1144.

Dahl, L.K., 1958. Salt intake and salt need. N. Engl. J. Med., 258: 1152–1157.

Dahl, L. K., 1960a. Possible role of salt intake in the development of essential hypertension. In: K.D. Bock and P.T. Cottier (Editors), Essential Hypertension. An International Symposium. Springer-Verlag, Berlin and New York, pp. 53–65.

Dahl, L.K., 1960b. Salt, fat and hypertension. The Japanese experience. Nutr. Rev., 18: 97–99.

Dahl, L.K., 1961. Effects of chronic excess salt feeding. Induction of self-sustaining hypertension in rats. J. Exp. Med., 114: 231–236.

Dahl, L.K., 1968. Salt in processed baby foods. Am. J. Clin. Nutr., 21: 787–792.

Dahl, L.K. and Love, R.A., 1954. Evidence for relationship between sodium (chloride) intake and human essential hypertension. Arch. Inten. Med., 94: 525–531.

Dahl, L.K. and Love, R.A., 1957. Etiological role of sodium chloride intake in essential hypertension in humans. J. Am. Med. Assoc., 164: 397–400.

Dahl, L.K. and Schackow, E., 1964. Effects of chronic excess salt ingestion: Experimental hypertension in the rat. Can. Med. Assoc. J., 90: 153–160.

Dahl, L.K., Heine, M. and Tassinari, L., 1962. Effect of chronic salt ingestion: Evidence that genetic factors play an important role in susceptibility to experimental hypertension. J. Exp. Med., 115: 1173–1190.

Dahl, L.K., Heine, M., Leitl, G. and Tassinari, L., 1970. Hypertension and death from consumption of processed baby foods by rats. Proc. Soc. Exp. Biol. Med., 133: 1405–1408.

Dahl, L.K., Leitl, G. and Heine, M., 1972. Influence of dietary potassium and sodium/potassium molar ratios on the development of salt hypertension. J. Exp. Med., 136: 318–330.

Ebihara, A., 1972. Studies on the pathogenesis of experimental hypertension in rats. Jpn. Circ. J., 36: 603–605.

Ebihara, A. and Martz, B.L., 1970. Comparative effects of currently available antihypertensive agents on spontaneously and renal hypertensive rats. Am. J. Med. Sci., 259: 257–261.

Ebihara, A. and Martz, B.L., 1971. Observations on several experimental models of hypertension in mice. Jpn. Heart J., 12: 275–280.

Fallis, N., Lasagna, L. and Tetreault, L., 1962. Gustatory thresholds in patients with hypertension. Nature (London), 196: 74–75.

Freis, E.D., 1976. Salt, volume and the prevention of hypertension. Circulation, 53: 589–595.

Hatano, S., 1974. Hypertension in Japan: A review. In: O. Paul (Editor), Epidemiology and Control of Hypertension. Continental Medical Book Corp., New York, pp. 63–99.

Henkin, R.I., 1974. Salt preference in patients with essential hypertension and with hypertension due to primary hyperaldosteronism. J. Chronic Dis., 27: 235–244.

Issacson, L.C., Modlin, M. and Jackson, W.P.U., 1963. Sodium intake and hypertension. Lancet, Part 1: 946.

Louis, W.J., Tabei, R. and Spector, S., 1971. Effects of sodium intake on inherited hypertension in the rat. Lancet, Part 2: 1283–1286.

Maddocks, I., 1961. Possible absence of essential hypertension in two complete Pacific island populations. Lancet, 2: 396–399.

Maddocks, I., 1967. Blood pressures in Melanesians. Med. J. Aust., 1: 1123–1126.

Meneely, G.R. and Ball, C.O.T., 1958. Experimental epidemiology of chronic sodium chloride toxicity and protective effect of potassium chloride. Am. J. Med., 25: 713–725.

Meneely, G.R., Tucker, R.G. and Darby, W.J., 1952. Chronic sodium chloride toxicity in the albino rat. I. Growth on a purified diet containing various levels of sodium chloride. J. Nutr., 48: 489–498.

Meneely, G.R., Tucker, R.G., Darby, W.J. and Auerbach, Sh.H., 1953. Chronic sodium chloride toxicity in the albino rat. II. Occurrence of hypertension and of a syndrome of edema and renal failure. J. Exp. Med., 98: 71–80.

Mori, M., Kawada, T. and Torii, K., 1991a. Appetite and taste preference in growing rats given various levels of protein nutrition. Brain Res. Bull., 27: 417–422.

Mori, M., Kawada, T., Ono, T. and Torii, K., 1991b. Taste preference and protein nutrition and L-amino acid homeostasis in male Sprague-Dawley rats. Physiol. Behav., 49: 987–995.

Okamoto, K. and Aoki, K., 1963. Development of a strain of spontaneously hypertensive rats. Jpn. Circ. J., 27: 282–293.

Okamoto, K., Tabei, R., Fukushima, M., Nosaka, S., Yamori, Y., Ichijima, K., Haebara, H., Matsumoto, M., Maruyama, T., Suzuki, Y. and Tamegai, M., 1966. Further observations of the development of strain of spontaneously hypertensive rats. Jpn. Circ. J., 30: 703–716.

Oliver, W.J., Cohen, E.L. and Neel, J.V., 1975. Blood pressure, sodium intake, and sodium related hormones in the Yanomano Indians, a "no-salt" culture. Circulation, 52: 146–151.

Page, L.B., 1976. Epidemiologic evidence on the etiology of human hypertension and its possible prevention. Am. Heart J., 91: 527–534.

Page, L.B., Damon, A. and Moellering, R.C., 1974. Antecedent of cardiovascular disease in six Solomon Islands societies. Circulation, 49: 1132–1146

Pauque, C., 1980. Sahara bedouins and the salt water of the Sahara: A model for salt intake. In: M.R. Kare, M.J. Fregly and R.A. Bernard (Editors), Biological and Behavioral Aspects of Salt Intake. Academic Press, New York, pp. 31–47.

Prior, L.A., Evans, J.G., Harvey, H.P.B., Davidson, F. and Lindsey, M., 1968. Sodium intake and blood pressure in two Polynesian populations. N. Engl. J. Med., 279: 515–520.

Sasaki, N., 1964. The relationship of salt intake to hypertension in the Japanese. Geriatrics, 19: 735–744.

Schechter, P.J., Horwitz, D. and Henkin, R.I., 1973. Sodium chloride preference in essential hypertension. J. Am. Med. Assoc., 225: 1311–1315.

Schechter, P.J., Horwitz, D. and Henkin, R.I., 1974. Salt preference in patients with untreated and treated essential hypertension. Am. J. Med. Sci., 261: 320–326.

Swaye, P.S., Gifford, R.W. and Berrettoni, J.N., 1972. Dietary salt and essential hypertension. Am. J. Cardiol., 29: 33–38.

Tabuchi, E., Ono, T., Nishijo, H. and Torii, K., 1991. Amino acid and NaCl appetite, and LHA neuron responses of lysine-deficient rat. Physiol. Behav., 49: 951–964.

Thomas, C.B., 1973. Genetic patterns of hypertension in man. In: G. Onesti, K.E. Kim and J.D. Moyer (Editors), Hypertension: Mechanisms and Management. Grune and Stratton, New York, pp. 67–73.

Torii, K., 1980. Salt intake and hypertension in rats. In: M.R. Kare, M.J. Fregly and R.A. Bernard (Editors), Biological and Behavioral Aspects of Salt Intake. Academic Press, New York, pp. 345–366.

Torii, K., Mimura, T. and Yugari, Y., 1986. Effects of dietary protein on the taste preference for amino acid in rats. In: M.R. Kare and J.G. Brand (Editors), Interaction of the Chemical Senses with Nutrition. Academic Press, New York, pp. 45–69.

Torii, K., Mimura, T. and Yugari, Y., 1987. Biochemical mechanism of umami taste perception and effect of dietary protein on the taste preference for amino acids and sodium chloride in rats. In: Y. Kawamura and M.R. Kare (Editors), Umami: A Basic Taste. Marcel Dekker, New York, pp. 523–563.

Tordoff, M.G., 1992. Influence of dietary calcium on sodium and calcium intake of spontaneously hypertensive rats. Am. J. Physiol., 262. (in press).

Tordoff, M.G., Ulrich, P.M. and Schulkin, J., 1990. Calcium deprivation increases salt intake. Am. J. Physiol. 259: R411–R419.

Tucker, R.G., Ball, C.O.T., Darby, W.J., Early, W.R., Kory, R.C., Youmans, J.B. and Meneely, G.R., 1957. Chronic sodium chloride toxicity in the albino rat. III. Maturity characteristics, survivorship, and organ weights. J. Gerontol., 12: 182–189.

Wotman, S., Mandel, I.D., Thompson, R.H. and Laragh, J.H., 1967. Salivary electrolytes and salt taste thresholds in hypertension. J. Chronic Dis., 20: 833–840.

Zinner, S.H., Levy, P.S. and Kass, E.H., 1971. Familial aggregation of blood pressure in childhood. N. Engl. J. Med., 284: 401–404.