Enhanced Salt Toxicity in the Spontaneously Hypertensive Rat (35312)

JEANNE A. BARSANTI, HAROLD R. C. PILLSBURY III, AND EDWARD D. FREIS
Veterans Administration Hospital and the Department of Medicine, Georgetown University School of Medicine, Washington D.C. 20422

In 1950, Sapirstein *et al.* (1) demonstrated that rats developed hypertension when given 2% NaCl solution to drink for 6 weeks. Dahl *et al.* (2, 3) developed two strains of Sprague-Dawley rats, one of which became hypertensive rapidly when fed an excess salt diet while the other was resistant to salt. These two strains remained consistent as hypertension-sensitive and hypertension-resistant with other methods of creating experimental hypertension, such as clipping one renal artery (4). In 1963, Okamoto and Aoki (5) produced by selective inbreeding a spontaneously hypertensive strain of Wistar rats (SHR) whose members developed elevated blood pressures as they matured. Louis *et al.* (6) tested the effect of salt consumption on this SHR strain and concluded that their blood pressures were relatively unresponsive to excessive sodium intake. Such a result is at variance with the experience of Dahl and also is inconsistent with Okamoto's observations that SHR responded with a greater rise in blood pressure than control rats when given DOCA plus 1% NaCl for 10 weeks or following unilateral nephrectomy (7). The present study was undertaken to reexamine the question as to whether SHR developed more severe hypertension than normal (non-SH) Wistar rats when subjected to a prolonged period of excess salt ingestion.

Methods. Six male and 8 female SHR derived from the strain developed by Okamoto and Aoki were divided into two groups each consisting of 4 females and 3 males. The membership of the groups was determined by matching average systolic pressures and body weights. One group received 1% NaCl in tap water *ad libitum* while the control group was given plain tap water. All rats ate Wayne chow. They were housed in plastic cages, three males or four females to a cage. Two control groups of 3-month-old normal (non-SH) Wistar rats were also formed. Three males and three females received the 1% NaCl solution while one female and two males received tap water without excess salt.

All rats were kept in a room controlled at a constant temperature of 78°F. Systolic blood pressures were recorded approximately every 2 weeks in this room by means of a tail cuff and mercury-in-rubber resistance gauge. The inflatable cuff was connected to a Statham transducer attached to a Hewlett-Packard carrier preamplifier and 2-channel recorder. The other channel of the recorder was connected through another preamplifier and a small Wheatstone bridge to the resistance gauge which detected the change in tail circumference occurring at the time of the first pulse appearing distal to the tail cuff. The rats were lightly anesthetized with ether during pressure measurements. The animals were weighed every 2 weeks.

Results. Water consumption. SH rats receiving 1% salt solution drank 2 to 3 times more than those on tap water from the third week and 1 to 3 times more than the normal rats on the same salt regimen (Table I). Water consumption in the SH rats receiving salt increased with time until the majority had died. Normal rats receiving excess salt drank less than double the amount consumed by their litter mates who were on tap water.

Mortality. Three of the 4 female SHR, drinking 1% NaCl, died between the weeks 18 and 21 of the study. One male SHR, receiving 1% salt water, died in week 14 and another of the same group died in week 19. One SHR male and one SHR female are still alive after 28 weeks on the high salt regimen. All SHR who received tap water without

TABLE I. Average Water Consumption (ml/rat/day) in Various Groups.

Time in study (weeks)	SHR				Normal rats			
	Controls (tap water)		1% NaCl		Controls (tap water)		1% NaCl	
	Male	Female	Male	Female	Male	Female	Male	Female
3	44	27	92	64	32	21	46	38
4	59	30	118	66	31	12	50	45
5	44	25	101	61	34	12	49	58
9	42	25	148	68	—	25	44	42
14	34	21	176	128	—	—	—	—
19	40	—	110	139	—	—	—	—
20	—	—	—	—	25	17	28	25
21	39	25	111	84	—	—	—	—

excess salt are alive with the exception of one female who was accidentally over-etherized in week 26. One normal Wistar female receiving 1% NaCl died in week 19. All of the other normal rats remained alive and in good health through 20 weeks.

Weights. Comparing the same sexes, both SHR groups showed the same growth rates except when an individual in the salt group was approaching death. Such rats would usually show a slight weight gain followed by a rapid and substantial weight loss (Fig. 1). Both groups of normal rats grew at the same rate until week 7 when the males and females receiving salt began to grow more slowly. With the exception of the females receiving salt, the normal rats grew faster than the SHR on similar regimens.

Blood pressures. By the week 3 after beginning the study the average blood pressure of all SHR on the higher salt regimen was greater than that of their tap water counterparts (Table II). By week 9 this difference was significant ($p<.01$) and remained significant through week 20 ($p<.005$) after which time most of the rats receiving excess salt died and the levels of the blood pressures of the remaining control rats began to reach that of the two remaining rats on excess salt (Table II). No significant differences were found between the normal control rats receiving 1% salt and those receiving tap water.

Pathology. Prior to death the SH rats receiving excess salt had a scruffy, ragged appearance. Later they developed abdominal bloating, edema of the front and the back legs, and decreased motor activity. Terminally, these rats showed rhythmic twitching movements and labored breathing.

The SH rats receiving excess salt also had periarteritis of the mesenteric vessels. The kidneys were small and presented granular surfaces. Two of these rats, one male and one female, had left ventricular scarring. All five rats that died showed left ventricular hypertrophy. The control SHR (sacrificed at 27

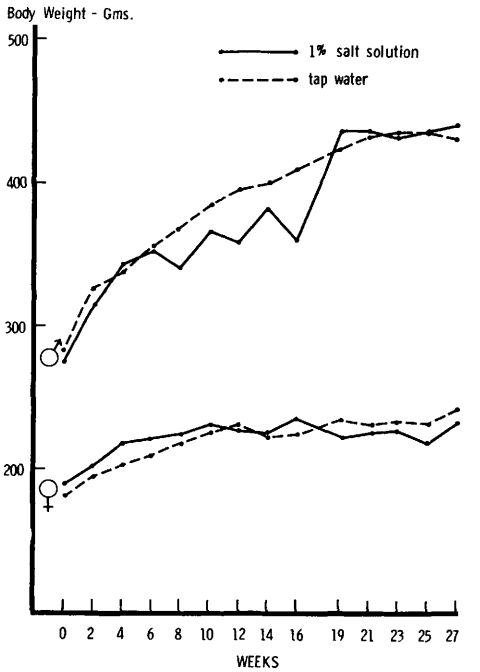

FIG. 1. Changes in body weight of SH rats on tap water (- -); or 1% salt (—) during study period. Males shown above and females below.

TABLE II. Blood Pressure Changes in Various Groups of Rats.

	Systolic blood pressure (mm Hg)			
	SHR		Normal	
Time in study (weeks)	Controls (tap water)	1% NaCl	Controls (tap water)	1% NaCl
0	121 ± 17	120 ± 23	107 ± 8	106 ± 15
1	136 ± 14	129 ± 14		
3	142 ± 23	144 ± 25	111 ± 12	104 ± 18
5	152 ± 28	169 ± 26		
7	152 ± 20	167 ± 23		
9	148 ± 14	184 ± 31	91 ± 5	105 ± 16
15	155 ± 20	196 ± 14	106 ± 11	103 ± 19
20	153 ± 19	186 ± 2	104 ± 8	103 ± 10
24	146 ± 19	176 ± 12		
26	172 ± 18	179 ± 6		
28	160 ± 26	185 ± 33		

weeks) displayed none of the above changes. The female normal rat which died had no hypertension or edema and apparently died of a respiratory infection.

Histological examination of the kidneys of the SH rats, given 1% salt solution who died, disclosed the typical changes of malignant nephrosclerosis with fibrinoid necrosis of the media and intimal hyperplasia of the renal arterioles. The control SHR given tap water showed a normal renal architecture on histological examination. All of the normal Wistar rats were sacrificed between weeks 20 and 21. No abnormalities were found in the heart, mesentery, or kidneys of these rats.

Discussion. Many investigators have described the pathology of the accelerated phase of hypertension in rats to be rapid with loss of weight, edema, apathy, twitching or convulsions, and death (9–13). Renal damage shown by granular outer surfaces and a thin and indistinct cortical layer on cut section is common as is cardiac hypertrophy and periarteritis. The rats also may have fibrotic areas in the myocardium. Histological examination shows fibrinoid necrosis of the renal arterioles. These pathological changes developed only in the SHR on 1% salt and were not seen in the normal rat or SHR on tap water during the period of the experiment.

In the study of Meneely and associates (9), 18% of their rats fed 7, 8.4, or 9.8% NaCl died between months 3 and 6. In Koletsky's study (11) 40 weeks were required on 1% NaCl to produce well-developed hypertension in normal rats compared with 9 weeks for a significant elevation of blood pressure in our SH rats.

The present results are similar to those of Dahl (4) in which his "salt-sensitive" rats, while developing hypertension more slowly when initiation of a high salt diet was delayed until the rats were 3 months old, still showed an increased blood pressure and death within 8 months or less. Louis and his associates (6) concluded that the SH rat shows a relative insensitivity of its hypertension to changes in dietary sodium. However, their observations on salt-loaded rats did not extend beyond 10 weeks; and after 7 weeks the blood pressure was significantly higher in the SH rats given excess salt. Therefore, their results do not differ greatly from the present observations.

Summary. Chronic ingestion of 1% salt solution causes accelerated hypertension leading to death in the SH rat at a more rapid rate than in the normal rat given 1% salt or in the SH rat given tap water.

1. Sapirstein, L. A., Brandt, W. L., and Drury, D. R., Proc. Soc. Exp. Biol. Med. 73, 82 (1950).

2. Dahl, L. K., Heine, M., and Tassinari, L., Nature (London) 194, 480 (1962).

3. Dahl, L. K., Heine, M., and Tassinari, L., J. Exp. Med. 115, 1173 (1962).

4. Dahl, L. K., Heine, M., and Tassinari, L., J. Exp. Med. **118**, 605 (1963).

5. Okamoto, K., and Aoki, K., Jap. Circ. J. **27**, 28 (1963).

6. Louis, W. J., Tabei, R., Spector, S., and Sjoerdsma, A., Circ. Res. **14**, 15 (1969).

7. Okamoto, K., Int. Rev. Exp. Pathol. **7**, 227 (1969).

8. Dahl, L. K., Knudsen, K. D., Heine, M., and Leitl, G. J., Circ. Res. **22**, 11 (1968).

9. Meneely, G. R., Tucker, R. G., Darby, W. J., and Auerbach, S. H., J. Exp. Med. **98**, 71 (1953).

10. Okamoto, K., Aoki, K., Nosaka, S., and Lukushima, M., Jap. Circ. J. **30**, 703 (1966).

11. Koletsky, S., Lab. Invest. **7**, 377 (1958).

12. Smirk, F. H., and Phelan, E. L., J. Pathol. Bacteriol. **89**, 57 (1965).

13. Byrom, F. B. (F. Gross, ed.), p. 125. Springer-Verlag, New York (1966).

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