PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE 154, 30-32 (1977)

Failure of Sodium Iodide Loading To Inhibit Renin in the Rat (39596)

JOHN H. GALLA, THEODORE A. KOTCHEN, AND ROBERT G. LUKE
Renal and Endocrine Divisions, Department of Medicine, University of Kentucky College of Medicine, Lexington, Kentucky 40506

Inhibition of renin secretion by NaCl administration has been attributed to detection of a signal in renal baroreceptors or at the macula densa (1). KCl (2), HCl (3), and $CaCl_2$ (4) inhibit renin release, and active Cl transport has been demonstrated in the ascending limb of Henle's loop (5). These observations among others have led to the hypothesis that chloride may be a principal ion signaling alterations in renin release at the macula densa (6). We have demonstrated that $NaHCO_3$ and $KHCO_3$ loading fail to inhibit renin in the rat, supporting the hypothesis that the signal produced at the macula densa may be modified substantially by the anion delivered with Na or K (7). We have extended these studies by comparing the renin response in the rat to chronic loading with equimolar amounts of NaI or NaCl.

Methods. Twenty-four adult male Sprague–Dawley rats were given free access to deionized water and a low NaCl feed (International Clinical and Nuclear Corp., Cleveland, Ohio) for 1 week. This feed contains 274 μEq of K^+, 1 μEq of Na^+, and 2 μEq of halide per g determined following nitric acid digestion in our laboratory. The animals were then divided into three groups of eight rats each and were placed in individual metabolic cages for the second week of the study. For drink, group A was given NaI, 75 mEq/liter; group B, NaCl 75 mEq/liter; and group C, deionized water. All animals continued on the low NaCl diet for the duration of the study. To assure a similar intake of feed and drink, group A rats were studied 1 day in advance of groups B and C, which were maintained according to a paired feeding schedule. Daily sodium, potassium, halide, and water balances were determined for each animal, based on measurement of dietary intake and urinary excretion.

After 7 days on this regimen, all animals were sacrificed by decapitation, and blood emanating from the trunk was collected in chilled EDTA-containing tubes for subsequent determinations of plasma renin activity (PRA) and urea nitrogen concentration. A single kidney was harvested from each animal for subsequent determination of renal renin content (RRC).

Na and K concentrations in feed and urine were measured by flame photometry and urea nitrogen by the method of Crocker (8). Total halide (Cl and I) was measured with a Buchler chloridimeter (Buchler Instruments, Ft. Lee, N.J.).

PRA was measured in quadruplicate with the radioimmunoassay procedure of Haber (9). Renal renin was extracted and quantified as previously described (10). One unit of renal renin is arbitrarily defined as that concentration of renin that will generate 100 ng of angiotensin I during a 15-min incubation in the presence of excess sheep renin substrate.

In instances where data were compared for two groups, statistical significance was determined with Student's t test. When data were compared among three groups and when the variance for the three groups was similar, the significance of group comparisons was computed with analysis of variances. Because analysis of variance requires similar group variances, for several three-group comparisons with dissimilar variances statistical significance was computed with the Wilcoxon rank sign test (11). Significance is at the 0.05 level.

Results. Initial and final body weights among the three groups did not differ (Table I). Plasma urea nitrogen concentration in group B was significantly different from ($P < 0.05$) that in group A, but neither was different from control.

Net fluid balance in groups A, B, and C did not differ (Table II). Net sodium balance was not significantly more positive ($P > 0.1$) in NaI-drinking animals than in those drinking NaCl and was greater than controls in both electrolyte-drinking groups. Net po-

tassium balance among the three groups did not differ ($P > 0.7$). Total halide balance was not different between the electrolyte-drinking rats but was significantly greater ($P < 0.01$) in both groups A and B than that for group C. Although the method for determining halide does not distinguish between chloride and iodide, it is likely that most of the measured halide excretion in group A represents iodide and in group B chloride.

PRA (4.0 ± 1.2 ng/ml/hr) in NaCl-drinking rats was suppressed significantly ($P < 0.05$) when compared to NaCl-deprived controls (7.9 ± 1.8 ng/ml/hr) (Fig. 1). However in NaI-drinking rats, PRA (9.8 ± 0.8) was not different from ($P > 0.1$) control values. RRC changed in the direction of the alterations in PRA but the magnitude of the change was not statistically significant ($P > 0.1$).

Discussion. Unlike dietary loading with NaCl, NaI loading failed to suppress PRA. Because there were no significant differences in initial and final body weights and water and sodium balance in NaI-drinking rats compared to NaCl-drinking rats, it seems unlikely that volume contraction in the former group can explain the failure of renin inhibition. Potassium balance was similar among the groups suggesting that failure of NaI to suppress renin is not related to an effect on potassium.

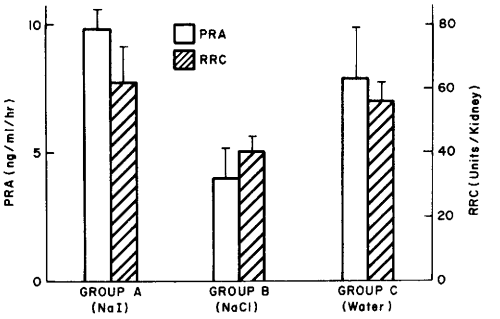

FIG. 1. PRA and RRC in groups A, B, and C.

RRC was not suppressed significantly by 7 days of loading with 0.075 *M* NaCl although, similar to PRA, RRC tended to be decreased in NaCl- but not in NaI-drinking animals. We have demonstrated previously that RRC in the rat is suppressed after 1 week of drinking 0.15 *M* NaCl (7). The present results suggest that, although PRA is suppressed, 0.075 *M* NaCl for 1 week in rats on a low sodium diet is not a sufficiently potent stimulus to inhibit RRC.

In the rat, active chloride transport has been demonstrated in the ascending limb of the loop of Henle (5), and the signal perceived by the macula densa during saline loading may be NaCl transport rather than Na load (12). Iodide is reabsorbed passively and coextensively with chloride in the nephron (13), and micropuncture studies have shown a lower permeability for iodide than for chloride in both the proximal and distal tubule of the rat (14, 15). However, in the presence of low chloride excretion

TABLE I. BODY WEIGHTS AND RENAL FUNCTION.[a]

Group	Initial body weight (g)	Final body weight (g)	Plasma urea nitrogen (mg/dl)
A (NaI) ($n = 8$)	313 ± 7	294 ± 9	27 ± 1*
B (NaCl) ($n = 8$)	311 ± 7	303 ± 8	20 ± 2
C (Water) ($n = 8$)	302 ± 6	291 ± 9	23 ± 1

[a] Values given are mean ± SE; n is indicated in parentheses. No statistical difference (P-NS) between or among groups unless indicated. * $P < 0.05$ compared to group B.

TABLE II. NET FLUID AND ELECTROLYTE BALANCE.[a]

Group	Fluid (ml/7 days)	Sodium (μEq/7 days)	Potassium (μEq/7 days)	Halide (μEq/7 days)
A (NaI) ($n = 8$)	45 ± 3	3062 ± 238*	3489 ± 895	1914 ± 162*
B (NaCl) ($n = 8$)	52 ± 6	2336 ± 306*	3782 ± 646	2119 ± 302*
C (Water) ($n = 8$)	46 ± 7	−68 ± 45	3984 ± 836	33 ± 29

[a] Values given are mean ± SE; n is indicated in parentheses. No statistical difference (P-NS) between or among groups unless indicated. * $P < 0.01$ compared to group C.

rates (a condition likely to be present in group A and group C animals of the present studies), Walser and Rahill provided evidence for active iodide transport (13). The failure of NaI to inhibit renin is consistent with the hypothesis that Na-induced inhibition of renin is mediated by NaCl transport across the macula densa. The demonstration that iodide cannot substitute for chloride in this role suggests that the active transport process for chloride at the macula densa is highly specific.

Summary. NaCl-deprived rats given NaI to drink failed to suppress PRA compared to rats drinking equimolar amounts of NaCl, despite a more positive Na balance in the former group. Volume contraction and potassium deficiency do not appear to explain this observation. If chloride is a principal ion to signal the macula densa to release renin, our data suggest that iodide cannot substitute in such a role.

1. Davis, J. O., Circ. Res. **218,** 301 (1970).
2. Flamenbaum, W., Kleinman, J. G., McNeill, J. S., Hamburger, R. J., and Kotchen, T. A., Amer. J. Physiol. **229,** 370 (1975).
3. Lifschitz, M. D., and Earley, L. E., Abst. Amer. Soc. Clin. Invest., p. 47a (1974).
4. Kotchen, T. A., Maull, K. I., Luke, R. G., Rees, D., and Flamenbaum, W., J. Clin. Invest. **54,** 1270 (1974).
5. Burg, M. B., and Green, N., Amer. J. Physiol. **224,** 659 (1973).
6. Schneerman, J., Clin. Nephrol. **3,** 74 (1975).
7. Kotchen, T. A., Galla, J. H., and Luke, R. G., Amer. J. Physiol. **231,** 1050 (1976).
8. Crocker, C. L., Amer. J. Med. Technol. **33,** 361 (1967).
9. Haber, E., Koerner, T., Page, L. B., Kliman, B., and Purnode, A., J. Clin. Endocrinol. Metab. **29,** 1349 (1969).
10. Flamenbaum, W., Kotchen, T. A., Nagle, R., and McNeill, J. S., Amer. J. Physiol. **224,** 305 (1973).
11. Snedecor, G. W., and Cochran, W. G., "Statistical Methods," 6th ed. Iowa State University Press, (1967).
12. Freeman, R. H., Davis, J. O., Gotshall, R. W., Johnson, J. A., and Spielman, W. S., Circ. Res. **34,** 307 (1974).
13. Walser, M., and Rahill, W. J., J. Clin. Invest. **44,** 1371 (1965).
14. Danielson, B. G., Persson, E., and Ulfendahl, H. R., Acta Physiol. Scand. **78,** 347 (1970).
15. Danielson, B. G., Persson, E., and Ulfendahl, H. R., Acta Physiol. Scand. **78,** 399 (1970).

Received June 2, 1976. P.S.E.B.M. 1977, Vol. 154.