Renal Renin in Unilaterally Nephrectomized Hypertensive Rats.* (30077)

EDWIN R. FISHER, M. TAMURA AND G. M. C. MASSON
Departments of Pathology, University of Pittsburgh and VA Hospital, Pittsburgh, Pa., and Research Division, Cleveland Clinic Foundation, Cleveland, Ohio

Hypertension produced by unilateral renal artery constriction is associated with an increase in renin content in the affected kidney and a decrease in the contralateral member. Since studies have shown close correlation between renal renin content and secretion (1,2), the elevation in the clipped kidney is often considered as evidence that renal hypertension is related to hyperactivity of the renal pressor system. However, contrary to this view is the observation that renal renin is not elevated in the clipped kidney of unilaterally nephrectomized rats which also exhibit hypertension(2,3). It has been suggested that in intact rats with unilateral renal artery constriction the untouched kidney may either inactivate renin and/or angiotensin or elaborate an antagonistic humoral factor both of which could stimulate renin production in the clipped kidney(2). Removal of this influence as in the situation of renal artery constriction in unilaterally nephrectomized rats would then account for the unaffected renin content in the remaining kidney.

We have previously demonstrated the sensitivity of renal renin content in ischemic and untouched kidneys of hypertensive rats to alterations in sodium state(4). Further, split-renal function studies in humans with renal hypertension have disclosed a reduction in sodium excretion by affected as compared to contralateral kidneys(5). It is well recognized that sodium retention results in a reduction of renal renin. This information prompted us to explore the possible influence of altered sodium intake on the relatively normal renin content of clipped kidneys of unilaterally nephrectomized rats with hypertension.

Methods. Seventy-one adult female Wistar rats weighing 150-175 g survived the experiment. All were subjected to unilateral nephrectomy and divided into 6 groups. Animals of Groups A and B were depleted of sodium by peritoneal dialysis, those of Groups C and D were given excess salt in the form of 1% NaCl solution as drinking fluid and those of Groups E and F were given tap water to drink. In addition animals of Groups A, C and E were subjected to partial constriction of the renal artery of the remaining kidney and those of Groups B, D and F to a sham operation.

All animals were maintained with a regular laboratory ration except those subjected to peritoneal dialysis (Groups A, B). These received a sodium deficient diet (General Biochemicals Co., Chagrin Falls, Ohio) and deionized water as drinking fluid.

Peritoneal dialysis was performed by withdrawal of 12 ml of peritoneal fluid 3 hours after injection of 25 ml of 5% glucose in water. This resulted in removal of 10-20 meq/l of sodium.

Blood pressure was estimated by a microphonic method prior to and at weekly intervals after operation. Animals were sacrificed 4 weeks after start of the experiment by aortic puncture.

Portions of kidney were fixed in Helly's fluid and sections stained for estimation of degree of granularity of juxtaglomerular cells (JGI) according to the method of the Hartrofts(6). Renal pressor activity was assayed by injection of kidney homogenates into the femoral vein of an anesthetized rat subjected to bilateral nephrectomy 24 hours previously(7). The height of pressor response was referred to a dose response curve obtained under similar conditions with a standard preparation of hog renin. Results were expressed in Goldblatt units per g of kidney.

Heart and adrenals were blotted and weighed. Frozen sections of the latter were stained with oil red O after fixation in 10% formalin and width of the zona glomerulosa expressed as percentage of cortex (ZGI).

Results. Sodium depletion or administra-

* Supported by U.S.P.H.S. Grant C-5195.

tion of 1% saline failed to influence significantly the degree of hypertension observed in unilaterally nephrectomized rats with subtotal constriction of the renal artery of the remaining kidney ($P>0.1$) (Table I). JGI and renal pressor activity were comparable in hypertensive rats not subjected to altered sodium intake and in normotensive controls ($P>0.1$) (Fig. 1); they were significantly increased ($P<0.01$) in hypertensive and normotensive animals subjected to sodium depletion, and decreased in hypertensive rats receiving 1% saline as drinking fluid. Normotensive controls receiving the latter exhibited normal JGI and renal pressor activity.

No significant difference in adrenal weights was observed in any group (Table I). ZGI paralleled changes observed in JGI and renal pressor activity. Heart weights were significantly elevated in all hypertensive animals.

Approximately 20% of all hypertensive animals, regardless of sodium intake, exhibited vascular and cardiac lesions as described in detail elsewhere(7).

Serum sodium was slightly but significantly ($P<0.05$) decreased in rats with restricted sodium intake and increased ($P<0.05$) in hypertensive rats receiving 1% saline.

Comment. Lack of effect of sodium depletion or salt-overload on degree of hyperten-

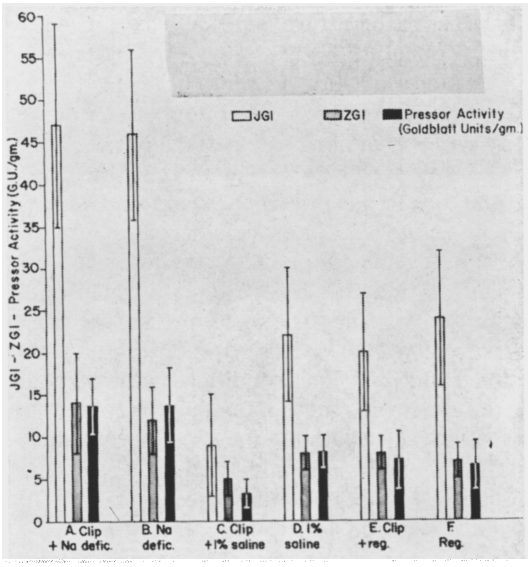

FIG. 1. Effect of sodium state on JGI, renal pressor activity and ZGI of unilaterally nephrectomized rats.

TABLE I. Blood Pressure, Heart and Adrenal Weights and Serum Na and Cl in Unilaterally Nephrectomized Rats.

Groups	No.	Blood pressure (mm Hg) 0	1 wk	2 wk	3 wk	4 wk	Heart (mg)	Adrenals (mg)	Na (meq/l)	Cl (meq/l)
A. Na defic + clip	9	94 ± 11*	144 ± 21	135 ± 18	137 ± 13	148 ± 12	920 ± 70	55 ± 10	137 ± 4	106 ± 4
B. Na defic	9	98 ± 12	114 ± 16	108 ± 14	101 ± 20	100 ± 10	720 ± 120	50 ± 14	136 ± 7	116 ± 4
C. 1% Na Cl + clip	8	90 ± 8	113 ± 26	132 ± 15	135 ± 13	158 ± 16	824 ± 60	48 ± 5	147 ± 2	107 ± 2
D. 1% Na Cl	9	83 ± 7	98 ± 14	101 ± 12	108 ± 13	108 ± 9	656 ± 54	46 ± 7	142 ± 4	102 ± 2
E. Clip + regular diet	9	95 ± 13	122 ± 21	132 ± 25	136 ± 13	153 ± 25	960 ± 80	52 ± 11	142 ± 3	107 ± 4
F. Regular diet	15	96 ± 15	95 ± 16	93 ± 14	96 ± 12	95 ± 15	740 ± 60	50 ± 10	142 ± 6	113 ± 4

* Standard deviation.

sion encountered in unilaterally nephrectomized hypertensive rats coincides with our previous observations on the relationship of sodium intake to blood pressure in intact rats with renal hypertension(4). Sensitivity of renin content in the clipped kidney of unilaterally nephrectomized rats to alterations of sodium state was also evident. These data are consonant with the view that the normal renin content of clipped kidneys of hypertensive unilaterally nephrectomized rats might be a reflection of sodium metabolism in such animals. Since sodium excretion has been demonstrated to be diminished in the affected kidney in instances of renal hypertension(5), it is not unexpected that removal of the contralateral more efficient kidney would provide for a greater degree of sodium retention and consequently less renal renin than is observed in clipped kidneys of intact rats. Although one might expect a more pronounced depression of renal renin in such animals, it is pertinent to note that in our experience with Wistar rats reactivity of the renin-angiotensin-aldosterone mechanism to salt overload is sluggish and often of slight magnitude. Administration of 2% saline to otherwise untreated rats for as long as 10 weeks fails to influence JGI and related parameters of this system. The effectiveness of exogenous salt overload to alter renal renin requires the existence of additional or predisposing salt-retaining states of modalities such as administration of DOCA, induction of nephrotic state or hypertension. As demonstrated in this study, administration of 1% saline to unilaterally nephrectomized controls was without effect on renal renin, whereas a profound change was noted in hypertensive members. On the other hand, the method of sodium depletion utilized appears sufficient to produce comparable increases in renal renin in both control and hypertensive animals.

The parallel changes in width of zona glomerulosa and JGI and renal pressor activity may be considered as morphological evidence for existence of the renin-angiotensin-aldosterone mechanism in the experimental situations studied. However, it becomes apparent that a significant dispartiy between the apparent activity of this system and renal hypertension exists. This information, together with other reports indicating the ability to induce renal hypertension in renin-depleted rats(8), and failure to discern increased circulating renin in chronic renal hypertension(9) provoke skepticism concerning a causal or direct quantitative relationship between the renin-angiotensin-aldosterone mechanism and blood pressure elevation in renal hypertension.

Summary. Juxtaglomerular index, renal pressor activity and width of the zona glomerulosa were normal in unilaterally nephrectomized hypertensive rats maintained on a normal sodium intake, increased in those subjected to sodium depletion and decreased in those receiving 1% saline. This indicates that renin formation and secretion are most likely the result of the sodium state of the animal rather than loss of a renin-stimulating agent in the contralateral or unclipped kidney. Failure of sodium to influence the degree of hypertension in unilaterally nephrectomized hypertensive rats militates against a direct quantitative relationship between blood pressure and the renin-angiotensin-aldosterone system.

1. Omae, T., Masson, G. M. C., Page, I. H., Am. J. Physiol., 1960, v199, 637.

2. Schaechteln, G., Regoli, D., Gross, F., Am. J. Physiol., 1963, v205, 303.

3. Regoli, D., Hess, R., Brunner, H., Peters, G., Gross, F., Arch. int. Pharmacodyn, 1962, v140, 416.

4. Fisher, E. R., Klein, H. Z., Proc. Soc. Exp. Biol. and Med., 1963, v113, 37.

5. Stamey, T. A., Circulation Res., 1962, v11, 200.

6. Hartroft, P. M., Hartroft, W. S., J. Exp. Med., 1953, v97, 415.

7. Masson, G. M. C., Yagi, S., Kashii, C., Fisher, E. R., Lab. Invest., 1964, v13, 321.

8. Bing, J., Acta Path. et Microbiol. Scand., 1962, v56, 362.

9. Pritchard, W. H., Ormond, A. P., Jr., Koletsky, S., Proc. Soc. Exp. Biol. and Med., 1964, v117, 127.

Received January 8, 1965. P.S.E.B.M., 1965, v118.