Pressor Activity of Circulating Blood After Focal Infarction of the Kidney in the Rat[1] (34956)

ARTHUR GROLLMAN
(With the technical assistance of Joan DeBusk)
Experimental Medicine Laboratory, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas 75235

In the acute hypertension which follows drastic restriction of a renal artery in man (1), the dog (2), and the rat (3) a pressor agent has been demonstrated to be present in the venous effluent from the affected kidney. This pressor agent has been variously considered to be renin, the concentration of which is increased in the renal venous effluent under these conditions (2); angiotensin, the pressor effect of which resembles that induced by the renal venous effluent (3); or an unidentified new pressor agent (1). Focal infarction of the kidney is also followed by an acute rise in blood pressure which in the rat is not accompanied by an increase in renin secretion (4, 5).

The presently reported studies demonstrate the appearance of a pressor agent in the blood after focal infarction of the kidney in a concentration proportional to the observed rise in blood pressure and its gradual disappearance as the blood pressure declines. This pressor agent differs from renin and angiotensin in many ways.

Materials and Methods. Piebald rats reared in the laboratory (McCollum–Evans strain), 4–8 months of age, weighing 250–350 g, of either sex, were used. Acute hypertension was induced by focal infarction of the kidney as described by Loomis (6). Under ether anesthesia a posterior branch of the renal artery was ligated resulting in infarction of a wedge of tissue involving approximately 5–10% of the kidney substance. Arterial blood pressures were determined on the unanesthetized rat by the method of Williams, Harrison, and Grollman (7).

Blood for bioassay was obtained from series of 10 rats at 5-day intervals for 30 days after infarction of the kidney by incising the end of the tail and collecting the blood into a chilled tube coated with heparin. The blood was centrifuged immediately at 4°. In five rats blood was also obtained from the renal vein at daily intervals for 5 days through a catheter inserted through the abdominal vena cava under nembutal anesthesia. In using the latter procedure hypotension and ischemia of the kidney must be avoided in order to avoid stimulating the secretion of renin (5).

Angiotensin formed during the collection and centrifugation of the blood was removed by passing the plasma just prior to its bioassay through a column of Dowex 50W-X2 (Bio-Rad Labs.) as described by Scornik and Paladini (8) and Boucher *et al.* (9). The pressor activity of the effluent was determined by injection into a pentolinium-treated rat (under nembutal anesthesia) with alternate injections of synthetic angiotensin II as described previously (1, 10).

Results. As shown in Fig. 1A, the venous effluent from the kidney after infarction of the kidney exerts a pressor action similar to that observed in the human suffering from surgically remediable hypertension (1) or in the dog with a drastically restricted renal artery (2). The venous effluent obtained from the noninfarcted control kidney under the same conditions exerts no pressor activity as shown in Fig. 1B.

In Fig. 2 are shown the average pressor

[1] This investigation was supported in part by Grant HE-07916 from the National Institutes of Health, U.S. Public Health Service.

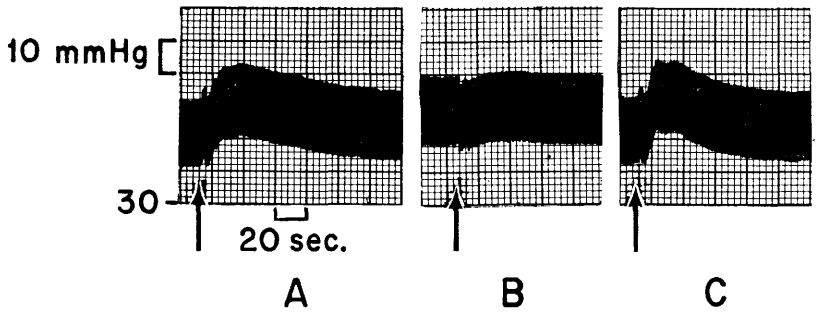

FIG. 1. Effect of focal infarction of the kidney on pressor action of its venous effluent. A. Pressor response to 0.25 ml plasma (after treatment with Dowex 50W-X2) from rat infarcted 1 week previously. B. Absence of pressor response from 0.25 ml of plasma from control uninfarcted kidney. C. Response to 1 ng angiotensin II in 0.25 ml normal saline.

activity (expressed as nanogram equivalents of synthetic angiotensin II) of the peripheral blood and the average blood pressure of a series of 10 rats after infarction of both kidneys. The close correlation of the pressor activity with the blood pressure is consistent with the view that the elevation in blood pressure is mediated through the liberation of a pressor agent by the kidney.

Although the observed pressor response (Fig. 1A) resembles that exerted by angiotensin, the removal of the latter by absorption with Dowex 50W-X2 indicates that it is not due to angiotensin, unless one assumes

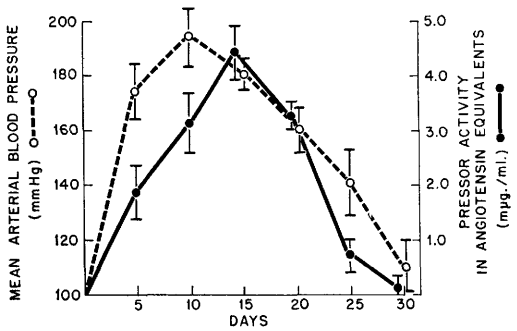

FIG. 2. Correlation of mean arterial blood pressure (mm Hg) and pressor activity of peripheral plasma (ng equivalents of angiotensin) after bilateral infarction of the kidneys. Each point of the curves is the average result obtained on 10 rats subjected to focal infarction of the left kidney. Abscissae represent days after the infarction. The vertical lines represent SE of the mean. Note the correlation of the pressor activity of the plasma (●—●) with the level of the blood pressure (O—O).

that angiotensin I or II under the condition of the experiment is secreted bound to a protein, for which there is no evidence. The absence of pressor activity from the control animals indicates that the appearance of the pressor agent is a consequence of the infarction which as shown previously (4, 5) is not accompanied by an increased secretion of renin.

Discussion. The presently reported studies demonstrate that the acute hypertension which follows focal infarction of the kidney in the rat is accompanied by the appearance of a circulating pressor agent elaborated by the kidney which resembles in action that previously reported in the human (1) and in the dog (2). Preoccupation with renin and angiotensin as renal pressor agents has led previous workers to assume that these agents mediated the acute elevation in blood pressure observed after drastic restriction of the renal artery. Although the concentration of renin in the renal venous effluent may be increased in patients with surgically remediable hypertension this is not always the case, and high levels of blood renin are encountered in the absence of hypertension as in cirrhosis of the liver, hyperplasia of the juxtaglomerular apparatus, etc. It would appear from the present and earlier studies from this laboratory (1, 2, 10) that a previously unrecognized pressor agent rather than renin is responsible for the hypertension observed after infarction of the kidney, drastic restriction of the renal artery, and other manipula-

tions which give rise to surgically remediable hypertension.

Although the pressor effect exerted by the renal venous effluent in acutely developing hypertension resembles that of angiotensin, it is still elicited after angiotensin has been removed from the plasma by dialysis or by adsorption on Dowex 50W-X2. In dogs, also, Scornik and Paladini (8) have shown that the increase in blood pressure which follows drastic restriction of the renal arteries occurs with normal or undetectable angiotensin blood levels. Although the renin content of the renal venous effluent is usually (but not always) increased after restriction of the renal artery in man (11) and the dog (2), this is not the case after focal infarction of the kidney in the rat (4, 5). Since such infarction may occasionally cause surgically remediable hypertension, reliance on the determination of the renin content of the renal venous effluent may fail to identify patients suffering from this disturbance (11).

As is the case in surgically remediable hypertension observed in man (1) and in acute hypertension induced by drastic restriction of the renal artery in the dog (2) and rat (3), removal of the infarcted kidney is followed by an immediate decline in the elevated blood pressure to normal levels (12). It differs in this respect from chronic hypertension induced by such procedures as moderate restriction of one renal artery or the application of a figure-of-eight ligature with ablation of the contralateral kidney which requires some weeks or months for its development. This is also the case in the various forms of chronic hypertension in the human which are not accompanied by the presence of a demonstrable pressor agent in the renal venous effluent and are not curable by nephrectomy.

Bilateral infarction of the kidneys, as shown by Loomis (6) or unilateral infarction with contralateral nephrectomy (5) results in the appearance ultimately of sustained hypertension rather than the temporary elevation in blood pressure noted in the present study. The development of chronic hypertension under these conditions has been attributed to an autoimmune reaction resulting in renal damage sufficient to interfere with that function of the kidney responsible for the maintenance of the normotensive state (12).

Summary. The pressor activity of the plasma of the renal venous effluent of rats rendered acutely hypertensive by focal infarction of the kidney has been demonstrated. The pressor effect is transient and is due to the elaboration of an agent which can be differentiated from renin and angiotensin. The rat, accordingly, resembles the dog and man in manifesting a form of acute hypertension which differs from chronic hypertension in being mediated by a previously unrecognized pressor agent elaborated by the kidney. As in the dog and man, the pressor agent may be demonstrated in the renal venous effluent. Its concentration in the peripheral blood is proportional to the observed elevation in blood pressure. The pressor effect and rise in blood pressure appear within a day after focal infarction of the kidney and last for about 30 days.

1. McPhaul, J. J., Jr., McIntosh, D. A., Williams, L. F., Grotti, E. J., Malette, W. G., and Grollman, A., Ann. Inter. Med. **61**, 847 (1964).

2. Ebihara, A. and Grollman, A., Amer. J. Physiol. **214**, 1 (1968).

3. Koletsky, S., Rivera-Velez, J. M Marsh, D. G., and Pritchard, W. H., Proc. Soc. Exp. Biol. Med. **125**, 96 (1967).

4. Omae, T., Masson, G. M., and Page, I. H., Circ. Res. **9**, 441 (1961).

5. Sokabe, H., and Grollman, A., Amer. J. Physiol. **205**, 264 (1963).

6. Loomis, D., Arch. Pathol. **41**, 231 (1946).

7. Williams, J. R., Jr., Harrison, T. R., and Grollman, A., J. Clin. Invest. **18**, 373 (1939).

8. Scornik, O. A. and Paladini, O. A., Amer. J. Physiol. **201**, 526 (1961).

9. Boucher, R., Veyrat, R., de Champlain, J., and Genest, J., Can. Med. Ass. J. **90**, 194 (1964).

10. Grollman, A., Can. Med. Ass. J. **90**, 299 (1964).

11. Grollman, A., and Ebihara, A., Texas Rep. Biol. Med. **26**, 313 (1968).

12. White, F. N., and Grollman, A., Nephron **1**, 93 (1964).

Received Feb. 11, 1970. P.S.E.B.M., 1970, Vol. 134.