Studies on the Pathogenesis of Experimental Hypertension in Rats*

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Although many papers have demonstrated a close relationship between renin and hypertension resulting from renal artery narrowing, few have appeared on the pathogenesis of such other types of experimental hypertension as that associated with renal hemi-infarct or following figure-of-eight ligation of the kidney. In this paper, the transmissibility of renal and congenital hypertension through the parabiotic junction was investigated in rats and the renin content was determined in parts of the kidneys of rats having renal hypertension.

MATERIALS AND METHODS

Experiment 1

Four-week-old male spontaneously hypertensive rats and male Wistar rats with the same age were used. Parabiotic connection was performed by suturing scapulae, muscles and skin, making a common peritoneal cavity. Each rat was uninephrectomized on the adjoining side at the time of their parabiosis operation. The following renal operation was performed in one partner of parabiosis 8 weeks after parabiosis operation. Renal artery stenosis was induced by ligation of the renal artery, using a guide wire. Hemi-infarct of the kidney was produced by ligating the posterior branch of the renal artery, being based on the technique described by Loomis.1

Systolic blood pressure was measured by the tail microphone method once every week without anesthesia after animals were warmed for 10 minutes in a heating box maintained at 39°C.

Experiment 2

Eight-week-old Wistar rats were divided into the following 3 groups—Loomis hypertensives, Grollman hypertensives and uninephrectomized controls.

In rats of the 1st group, hemi-infarct of the kidney was produced by the same technique as experiment 1, and contralaterally nephrectomized.

In animals of 2nd group, the mass of the left kidney was constricted by figure-of-eight ligation by the technique described by Grollman2 and contralaterally nephrectomized. Systolic blood pressure was determined once every week by the same method as in experiment 1. Animals were sacrificed 2 weeks, 8 weeks and 20 weeks after operation and the kidneys were removed for extraction of renin. The partially infarcted kidney was divided into infarcted, intermediate and normal appearing parts and the kidney with figure-of-eight ligation was divided into constricted and non-constricted parts. The renin was extracted by Haas-Goldblatt technique3 after removal of the medulla from each part of the kidney. Its pressor activity was determined from the blood pressure elevation following intravenous injection of the sample into the assay rat anesthetized with sodium phenobarbital.

RESULTS

Experiment 1

The 12-week observation indicated a significant elevation of the blood pressure in the uninephrectomized partners which were united in parabiosis with Wistar rats having renal artery constriction or hemi-infarct of the kidney. On

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In the other hand, in the parabiosis between spontaneously hypertensive rats and Wistar rats, the blood pressure observations indicated no increase of pressure in the Wistar rats and no interference with the normal progression of hypertension in the spontaneously hypertensive partners. When $^{131}$I tagged albumin was injected, a significant appearance of the radioactivity was observed in the blood of the partner rats in 30 minutes both in the instance of the combination of spontaneously hypertensive and normal Wistar rats and in the parabiosis between a rat with renal artery operation and a normotensive rat.

Experiment 2

The renin determination in parts of the kidney which was removed 2 weeks after operation revealed a marked elevation in the intermediate part of the partially infarcted kidney and in the constricted part of the kidney with figure-of-eight ligature. Marked reduction of the renin content was observed in the infarcted and the normal appearing parts of the kidney with hemi-infarct and in the non-constricted part of the kidney with figure-of-eight ligature. Each part of the kidney showed gradual reduction of renin content over 20 weeks' observation period. At the 8th postoperative week, no significant difference was observed in the intermediate part of the partially infarcted kidney and in the constricted part of the kidney with figure-of-eight ligature from the control kidney. At the 20th postoperative week, all parts of the kidney showed a significantly less renin content than the control kidney.

DISCUSSION

Parabiotic studies in rats indicated that the hypertension following renal artery constriction and that associated with renal hemi-infarct results in hypertension in the parabiotic partner. When spontaneously hypertensive rats were united with normotensive rats, no transmission or amelioration of the blood pressure was noted. It is interpreted that the hypertension resulting from main renal artery narrowing and from hemi-infarct of the kidney is mediated by humoral factor(s) but that the hypertension in spontaneously hypertensive rats is not mediated by a transmissible factor.

The results of renin studies indicated that the tissue renin content was significantly elevated in a part of the kidney which was removed from a rat with acute hypertension resulting from renal hemi-infarct or figure-of-eight ligature of the kidney. The histological examination revealed an ischemic appearance in parts with increased renin content. Hypergranularity of juxtaglomerular apparatus was observed in these parts of the kidney. Although these studies do not provide a definite information on the role of renin in the pathogenesis of hypertension, the results might suggest a relationship between renin and acute stage of these types of hypertension.

SUMMARY

Parabiotic studies in rats indicated that the hypertension induced by renal artery narrowing or renal hemi-infarct was transmissible through parabiotic junction, but that the hypertension in spontaneously hypertensive rats was not. The studies of renin revealed that the renin content was significantly elevated in the area adjoining to the infarcted part of kidney with hemi-infarct and in the constricted area of the kidney with figure-of-eight ligature at an early stage of hypertension, but that it reduced at a later stage of the hypertension.

Acknowledgement

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REFERENCES


DISCUSSION:

Chairman: MASATO MATSUNAGA, Kyoto Univ. H. SOKABE: Omoe et al. (1961) and Sokabe et al. (1963) reported on renin content and renin release of the infarcted kidney. T. OMAE: We did not find any increase in renin release into the renal vein from the infarcted kidney. However, renin might be released through lymph. A. EBIRARA: Koletsky observed an increased renin activity in the renal vein of the rat with multiple kidney embolism (Arch. Path. 85: 1, 1968). Many reports suggest increased renin release from partially infarcted kidneys both of human patients (Arakawa et al.: Arch. Int. Med. Japanese Circulation Journal Vol. 36, June 1972
125: 830; Morimoto et al.: South Med. J. 64: 528, 1971) and of experimental animals (Koletsky et al.: Arch. Path. 78: 24, 1964.).

T. SARUTA: Concerning the problem whether renin is released through renal vein or through lymph, I point out recent findings which revealed existence of abundant renin and angiotensin in renal lymph.

K. ARAKAWA: In the case of human renal infarction, plasma renin increase is transient and has no relation to the blood pressure.

T. KOKUBU: Dr. Ebihara studied renin content per gram of each part of the kidney. I would rather know renin content of the whole kidney.

A. EBHIARA: Total renin content of the kidney of the hypertensive rats showed no significant difference from that of the controls, two weeks after the operation; and it was reduced eight weeks or twenty weeks after the operation. I did not measure the renin content of the kidney in the parabiosis experiment.

Y. YAMORI: No detection of humoral pressor factor in the parabiosis experiment means no transmittable humoral factor in SHR. I obtained the same results as Dr. Ebihara's by parabiosis between SHR and a normotensive rat. Cortisone was given to prevent a development of nonspecific parabiosis hypertension, and the kidneys of the parabiosed animal were removed to assure successful humoral transmission. SHR maintained hypertension for a long period even without kidneys. Considering the lack of transmittable humoral factor, the kidney of SHR seems to play no important role in the positive pressor mechanism. (Jap. Circul. J. 35: 821, 1971)

A. EBHIARA: You are right. I mean that my experiment of parabiosis indicated that the hypertension of SHR is not mediated by a humoral substance which is transmittable through the parabiotic junction.

J. KIRA: As the humoral factor which transmitted renal hypertension, do you consider a pressor factor or an anti-pressor factor? Confusions in results so far obtained could be resolved by proposing a hypertension-inducing substance in the kidney, which would elevate the blood pressure in both of acute and chronic stages. On my opinion, renin is not an essential factor in renal hypertension. It is required to see whether the blood pressure would fall by removing the infarcted kidney and to determine plasma renin of the parabiotic partner in the chronic stage.

A. EBHIARA: The results of my experiment on renin content could also be explained by lack of such an antihypertensive substance as Grollman mentioned. The data of the experiment does not provide any definite information on the problem whether the chronic stage of the hypertension is also mediated by a humoral principle or not.

CHAIRMAN'S COMMENT: No transmittable humoral factor and no positive role of the kidney were found in SHR by a parabiotic technique. As to a humoral transmittable factor in experimental renin hypertension, Dr. Ebihara stressed partial increase in renin content of the infarcted or partially ischemic kidneys and considered a role of renin in the pathogenesis of this hypertension. However, still lacking is sufficient evidence for increased renin release from these kinds of kidneys and for its relation to the blood pressure. Whether renin-angiotensin system or some other humoral factor(s) is responsible for producing or sustaining renal hypertension remains to be further investigated.