EFFECT OF ANGIOTENSIN ON BLOOD PRESSURE
IN NORMAL AND CIRRHOTIC RATS

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Abstract—The pressor activity of graded doses and an infusion of angiotensin was studied in 9 normal and 9 cirrhotic rats. No significant difference (P>0.05) in the mean pressor response to angiotensin was found. The results have been discussed herein.

The intense vasoconstrictor and pressor properties of angiotensin have played an important role in its historical association with hypertension (1-5). In the last decade a considerable amount of evidence has accumulated to show that angiotensin is a trophic hormone regulating aldosterone secretion (6-8) and its level in plasma is increased in patients of cirrhosis with ascites, a condition of secondary hyperaldosteronism (9, 10). Gross and co-workers have reported that an i.v. injection of angiotensin in all species including humans produced a sharp rise in systemic arterial pressure, which returned to normal within few min (11). On the other hand, an i.v. infusion of angiotensin into normal humans caused a rise in arterial pressure which was maintained at an elevated level for days and only returned to pre-infusion level when the infusion was stopped (11). Thus it was established that infusion of angiotensin to normal humans produces a dose dependent rise in blood pressure, while infusion to cirrhotic patients showed a variable response. Pazourek et al. (12) recorded no change in pressor response to angiotensin in cirrhotic patients as compared to healthy subjects. On the other hand, Laragh (13), Laragh et al. (14) and Ames et al. (15) have reported a decrease in pressor response to angiotensin in patients of cirrhosis with ascites.

In view of the above contradictory observations, it was considered worthwhile to investigate further the pressor effects of angiotensin in rats with advanced cirrhosis.

MATERIALS AND METHODS
Eighteen male rats (9 normal and 9 cirrhotic) weighing between 250-300 g were anaesthetised with an i.p. administration of 25%, urethane (1.4 g/kg). The animals were kept in supine position on a surgical table and allowed to breathe naturally. The jugular vein was cannulated using a polythene tube. Heparin (200 units/100 g) was administered through the jugular vein. The carotid artery was cannulated and connected to a Condon’s rat blood pressure manometer. A rest period of 30 min was allowed so that the blood pressure would be stabilized. Graded doses of angiotensin (10, 20 and 40 ng) were given
through the jugular vein to obtain a dose response. An interval of 5-10 min was allowed between any two doses in order to prevent a tachyphylaxis. In addition, a continuous infusion of angiotensin (10 ng/min) was given for two min in all the experiments.

Cirrhosis of the liver was produced in male rats (200 g-300 g) by intragastric administration of carbon-tetrachloride at a dose of 0.15 ml/100 g biweekly for 13 weeks. A careful record of mortality was maintained during the period. The histopathology of the liver was carried out at the end of the experiments to ascertain the degree of cirrhosis. The liver of each animal was indeed cirrhotic by the end of 13 weeks. The degree of cirrhosis was graded, according to Manglic et al. (16) into three groups.

Grade I Cirrhosis: Macroscopically the livers showed a fine granularity on the surface with granules less than 1 mm in diameter. Microscopically, the early annular type of fibrosis was usually seen.

Grade II Cirrhosis: The surface of the livers of this grade showed coarse granules, ranging from 1 mm to 2 mm in diameter (Fig. 1). Microscopically, an annular type of cirrhosis plus thick fibrous septa and pseudolobule formation were seen.

Grade III Cirrhosis: The surface of the liver had very coarse granules, 2 mm or more in diameter. Microscopically, there was marked pseudolobule formation, with thick septa and collagenization of fibrous tissue (Fig. 2A and B).

In the present study, 2 out of the 9 cirrhotic rats were categorised under the grade II cirrhosis while remaining 7 cirrhotic rats were put under Grade III classification. Ascites was not evident.

RESULTS

Angiotensin in doses of 10 ng, 20 ng and 40 ng produced a rise in blood pressure in both groups, which was dose related. There was an immediate rise and then a fall in blood
pressure within half to one min. No tachyphylaxis was observed at these doses. Angiotensin when given as an infusion produced immediate rise in blood pressure which continued for the duration of infusion and decreased gradually after the infusion was stopped.

The control blood pressure in 9 normal rats under urethane anaesthesia was 76.0 ± S.E. 8.5 mmHg. An i.v. injection of 10 ng, 20 ng and 40 ng of angiotensin produced a mean rise of 8.1 ± S.E. 1.18, 13.0 ± S.E. 1.73 and 20.0 ± S.E. 0.87 mmHg respectively in blood pressure. Infusion of 100 ng of angiotensin per min for 2 min produced a rise in blood pressure of 17.7 ± S.E. 3.49 mmHg.

In 9 cirrhotic rats the control blood pressure was 73.0 ± S.E. 3.7 mmHg. The rise in blood pressure produced by 10 ng, 20 ng and 40 ng of angiotensin was 8.7 ± S.E. 0.93,
TABLE 1. Effect of angiotensin on blood pressure in normal and cirrhotic rats.

| Groups                  | No. of experiments | Pressor response to angiotensin (Mean ± S.E.) |
|-------------------------|--------------------|----------------------------------------------|
|                         |                    | 10 ng | 20 ng | 40 ng | Infusion |
| Normal*                 | 9                  | 8.10 ± 1.18 | 13.00 ± 1.73 | 20.00 ± 0.87 | 17.70 ± 3.49 |
| Advanced cirrhosis**    | 9                  | 8.70 ± 0.93 | 14.30 ± 1.47 | 19.10 ± 1.84 | 15.70 ± 2.75 |

* Control blood pressure was 76 ± 8.5 mmHg.
** Control blood pressure was 73 ± 3.7 mmHg.

** DISCUSSION **

Our findings suggest that angiotensin had the same pressor effect in the normal as well as in rats with advanced cirrhosis. The results are in agreement with Pazourek et al. (12) who have reported no change in pressor response to angiotensin in cirrhotic patients as compared to healthy persons, however, no explanation for this stable response has been given. Laragh (13), Laragh et al. (14) and Ames et al. (15) reported that cirrhotic patients with ascites showed a decreased pressor response to angiotensin probably due to high levels of circulating angiotensin in the blood of these patients which would produce tachyphylaxis. On the other hand Dalpaulu et al. (17) reported a decreased pressor response to i.p. administration of angiotensin in rats with fatty infiltration of the liver. These workers did not agree with the above investigators that this decrease in response...
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was due to tachyphylaxis. Our findings are not in agreement with those of Dalpalu et al. (17), perhaps due to the difference in the route of administration of angiotensin. Failure to observe the reduced pressor effects of angiotensin in cirrhotic rats in the present study, could be attributed to the fact that these animals, though in an advanced state of cirrhosis did not have marked fluid retention. There was no apparent ascites. In the present study, as experimental evidence of raised angiotensin level in the blood of these cirrhotic rats (with no apparent ascites) is lacking, the phenomenon of tachyphylaxis cannot be ruled out. Further investigation is required for elucidation.

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