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The effect of angiotensin I on renal blood flow in sheep

Injections of angiotensin I or angiotensin II into the renal artery of the dog are immediately effective in reducing renal blood flow (Halvorsen, Fasciolo & Calvo, 1959; Barac, 1962). But Ng & Vane (1967, 1968) found angiotensin I to have no immediate constrictor effect on the renal vessels of the dog, and to require conversion to angiotensin II in the pulmonary circulation to be effective. We now report the action of angiotensin I on renal blood flow in the sheep.

The angiotensin I used was synthetic asparaginyl^{1}-valyl^{5}-angiotensin I (Osborn, Pickens & others, 1970) which is the angiotensin I equivalent of the angiotensin II (Hypertensin). Both hormones were supplied by Ciba Ltd., Basle. When the angiotensin I was tested against the angiotensin II using the rat isolated colon (Regoli & Vane, 1964) in Tyrode solution in twelve experiments, the material was shown to contain less than 1% of angiotensin II.

Five Kerry Hill ewes 35 kg (s.d. = $\pm$ 2 kg) (Osborn, Hughes & others, 1969), had renal blood flow measured (Cohn & Gombos, 1965). Renal vein blood was withdrawn by a 105 A Gilford constant withdrawal pump, through a 103 IR Gilford cuvette densitometer. The dye curves were recorded on a Moseley 710 BM recorder and the areas under the curves estimated after extrapolation of the down stroke. Calibration was effected *in vitro* by adding various amounts of indocyanine green to renal vein blood.

The indocyanine green (0·25 mg in 2 ml saline) was injected into the renal artery over 1 s. As the internal volume of the catheter was 0·2 ml, 1·8 ml of the dye was injected into the artery. Blood was sampled from the renal vein at a constant rate before, during and after the injection of the dye until the extinction of the blood remained constant for 10 s.

The validity of the approach was tested with the angiotensin II in an experiment in which doses of 0·02–1·0 μg of the hormone were injected into the renal artery. Injections in all experiments were made as 5 ml solutions in saline followed immediately by a wash with 2 ml of saline over 2 s. Each injection of the hormone was followed 5 min later by 7 ml of saline given as a divided dose of 5 ml (over 5 s) and 2 ml (over 2 s).

The duration of the effect of 0·20 μg of angiotensin II was estimated by injecting the indocyanine green 6, 10, 15, 20, 30, 45 s and 1, 2 and 3 min after the end of the injection of the hormone. This dose and these times were chosen since about 10% of the cardiac output flows through each kidney and because previous studies in sheep had shown that 2 μg of angiotensin II injected into the left ventricle usually increased the blood pressure by 15–20 mm Hg, the pressor effect lasting for about 3 min. The results demonstrated that angiotensin II caused a significant reduction in renal blood flow within 10 s of the conclusion of the injection of the hormone; the effect was maximal at + 15 s and was well maintained for a further 30 s. Thereafter it gradually declined so that at + 3 min the flow had returned to normal.

These results indicated that a suitable time at which to inject the indocyanine green was 20 s after the administration of the hormone; further experiments were therefore made in the same animal in which the dye was injected 20 s after doses of 0·02, 0·05,

0·10, 0·20, 0·50 and 1·0 μg of angiotensin III. These amounts reduced the average control flow of 280 ml/min by 5, 10, 25, 40, 45 and 55% respectively.

Both angiotensins were used in the four other animals. The effect of angiotensin I on renal blood flow was shown to be dose-dependant in a similar manner to that for angiotensin II, in the first of these animals; a dose of 0·50 μg of angiotensin I produced a similar reduction in flow to that given by 0·20 μg of angiotensin II and the duration of its effect was similar. Six injections of 0·50 μg of angiotensin I and six of 0·20 μg of angiotensin II were therefore made in this animal and also in the three others; the injections were made in the sequence saline, angiotensin I, saline, angiotensin II and the indocyanine green was injected 20 s after the administration of the angiotensin. The control blood flow varied from 10–12 ml/kg min^{-1} and the average reduction in flow was comparable for the hormones used in these doses (40% after angiotensin I and 45% after angiotensin II; the s.d. was $\pm$ 5% of the mean in both cases). Analysis of variance (Fisher & Yates, 1948; Moroney, 1951) showed that both hormones gave a highly significant reduction in flow ($P < 0{\cdot}001$ in every experiment).

Our findings show that angiotensin I reduces renal blood flow in sheep within less than one circulation time which is 16 s but it is less effective than angiotensin II in this respect. From previous studies we have shown that only about 15% of a given dose of the angiotensins into the renal artery of sheep escapes into the general circulation. Thus, apart from its direct effect, a dose of 0·5· μg of angiotensin I would have produced little or no reduction in renal blood flow even had the portion which escaped immediate removal by the kidney been subsequently fully converted to angiotensin II in the pulmonary circulation.

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