SHORT COMMUNICATION

ACTION OF ANGIOTENSIN ANTAGONISTS AND ANTI-SERUM UPON THE PRESSOR RESPONSE TO RENIN: FURTHER EVIDENCE FOR THE LOCAL GENERATION OF ANGIOTENSIN II

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SUMMARY

1. Bilaterally nephrectomized rats were infused with a pressor dose of renin. The blood pressure was only partially restored to normal by sufficient angiotensin II antiserum to block the pressor response to exogenous angiotensin II.

2. A reduced pressor response still occurred when animals which had been pre-treated with angiotensin II antiserum were infused with renin.

3. Infusion of an angiotensin II antagonist (1-sarcosine-8-alanine angiotensin II) restored the blood pressure of both groups of animals to normal.

4. These observations support the hypothesis that renin generates angiotensin II at a local vascular level. This site is inaccessible to antisera, but accessible to the low-molecular-weight antagonist.

Key words: angiotensin II antisera, angiotensin II antagonist, renin, blood pressure.

Circulating levels of renin and angiotensin may not reflect the concentration of these substances at their major site of action, i.e. the blood vessel wall receptors. Thus in nephrectomized animals the pressor action of renin is present even after renin activity is no longer detectable in the circulation (Schaechtelin, Regoli & Gross, 1964). In addition, anti-renin antiserum is effective in blocking the activity of exogenous renin (Weiser, Johnson & Hoobler, 1969) whereas antiserum to angiotensin II is only partially effective in blocking the pressor response to renin (Bing & Poulson, 1970).

Although blood pressure in some experimental models of hypertension has proved resistant to angiotensin II antiserum, competitive antagonists of angiotensin II have proved to be more effective (Bumpus, Sen, Smeby, Sweet, Ferrario & Khosla, 1973).

These and other observations have led us to suggest that renin generates angiotensin at a

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local vascular level in a site not readily accessible to antiserum (Swales & Thurston, 1973). The purpose of the present study is to provide further evidence for such a mechanism by observing the action of an angiotensin II antagonist and antiserum upon the pressor responses to renin and angiotensin II.

MATERIALS AND METHODS

Antiserum to angiotensin II amide (Hypertensin; Ciba) was obtained at a single bleeding from a rabbit immunized according to the method of Goodfriend, Fasman, Kemp & Levine (1966). One millilitre of this antiserum has been shown to neutralize the pressor action of 15:55 μmol (16 000 ng) of angiotensin II amide in the rat by using the method of Eide & Aars (1970). It has also been shown to be equally effective in blocking equipressor quantities of rat angiotensin (prepared by incubating rat plasma) and synthetic angiotensin II amide (J. D. Swales & H. Thurston, unpubl. observations). The angiotensin antagonist was l-sarcosine-8-alanine angiotensin II (Pals, Masucci, Denning, Sipos & Fessler, 1971).

Twenty white Wistar rats of both sexes weighing 180–300 g were used. Six to 24 h after bilateral nephrectomy (during which time the rats received water but no food) the jugular vein and carotid artery were cannulated under ether anaesthesia. Blood pressure was recorded by a Grass 79 polygraph recorder with a Statham transducer.

Nine rats (group 1) were injected with 0:2 unit of M.R.C. standard porcine renin intravenously. After 3 min, successive 0:1 ml volumes of antiserum were infused at approximately 1 min intervals until no further fall in blood pressure occurred and the pressor action of 49 nmol (50 ng) of angiotensin II amide was blocked (i.e. pressor response less than 5 mmHg). Six to 8 min after the injection of renin the antagonist was infused at a rate of 0.0095 μmol/min (10 μg/min) for 5 min.

The remaining eleven animals (group 2) received successive 0:1 ml volumes of antiserum until the pressor response to 49 nmol (50 ng) of angiotensin II amide was blocked. Each was then given 0:2 unit of M.R.C. standard porcine renin intravenously. The antagonist infusion was started 3 min later and again continued for 5 min.

All injections were given via the jugular cannula. The angiotensin II, renin and angiotensin antagonist were dissolved in saline (9°0 g/l).

RESULTS

Group 1. The mean (±SEM) base-line blood pressure for this group was 9:80±0:48 kPa (73:5±3:6 mmHg). The renin injection produced a mean rise of 6:49±0:59 kPa (48:7±4:4 mmHg). Infusion of antiserum caused a mean fall in blood pressure of 2:97±0:40 kPa (22:3±3:0 mmHg), with complete blocking of the pressor action of exogenous angiotensin II. Infusion of further doses of antiserum did not produce any further fall in pressure. A further fall occurred with the antagonist infusion, which restored the blood pressure to 10:93±0:58 kPa (82:0±4:4 mmHg) in 3–5 min, which does not differ significantly from the base-line value (P>0:05).

Group 2. The mean base-line blood pressure was 11:60±0:85 kPa (87:0±6:4 mmHg) before antiserum and 11:24±0:76 kPa (84:3±5:7 mmHg) afterwards (P>0:1). The higher initial pressure in this group was due to three animals with blood pressures more than 13:33 kPa
Angiotensin antagonists and antiserum (100 mmHg). Since these animals behaved in an identical fashion to the remaining eight rats, they have not been excluded. The mean blocking dose for this group of eleven animals was 0.44 ± 0.05 ml. Renin injection resulted in a mean rise in blood pressure of 2.99 ± 0.28 kPa (22.4 ± 2.1 mmHg), which was significantly less than in group 1 (P < 0.001). The antagonist infusion restored the blood pressure to 10.88 ± 0.69 kPa (81.7 ± 5.2 mmHg). This value does not differ significantly from the base-line value (P > 0.05).

No pressor response to these doses of angiotensin II or renin was elicited in either group after the antagonist was given. One animal was injected with renin and observed for 14 min, during which time the blood pressure decreased by 3 mmHg from the peak value.

DISCUSSION

In some situations renin appears to exert a pressor action independently of its presence in the circulation (Bing & Nielsen, 1973). The present results indicate that more readily diffusible angiotensin II antagonist inhibits the pressor effect of renin at a site which is not accessible to blocking by the relatively large molecules of angiotensin II antibody. Thus, although the antiserum totally blocked the pressor effect of a large dose of angiotensin II, a reduced blood pressure rise still occurred in response to renin. Blood pressure was lowered to base-line levels by the antagonist. When antiserum was infused after renin, only a partial fall in blood pressure occurred, despite complete blocking of the angiotensin II response.

These results may explain the resistance of rats with two kidney Goldblatt hypertension (Eide, 1972) to immunization against angiotensin II. It is noteworthy that the antagonist does appear to lower the blood pressure in this model (Pals et al., 1971). In renin-infused rats, the effectiveness of anti-renin antiserum (Weiser et al., 1969) and angiotensin antagonists support the concept of a renin-mediated blood pressure response which is independent of circulating angiotensin.

We have previously suggested that renin generates angiotensin II at the vascular level (Swales & Thurston, 1973); renin-like activity has been demonstrated in hog arterial wall (Gould, Skeggs & Kahn, 1964). More recently, Hayduk, Ganten, Boucher & Genest (1972) have demonstrated increased mesenteric artery wall renin in salt-depleted dogs. The proven contiguity of converting enzyme activity (Aiken & Vane, 1972) would allow local generation of angiotensin II at the arteriolar level if renin substrate also has access to this site.

We believe, therefore, that it is possible for the renin angiotensin system to maintain hypertension even in the absence of elevated circulating levels of angiotensin II.

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REFERENCES


