The role of sodium retention in Goldblatt 2-kidney hypertension in the rat

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Summary

1. Infusion of angiotensin II antagonist failed to restore the blood pressure of short-term Goldblatt 2-kidney hypertensive rats to normal levels before and after sodium restriction.
2. The blood pressure of both normal and sodium-restricted Goldblatt 2-hypertensive rats remained elevated 6 h after bilateral nephrectomy.
3. The residual hypertension found during antagonist infusion and after bilateral nephrectomy is not maintained by the renin–angiotensin system or sodium retention.

Key words: angiotensin II antagonist, bilateral nephrectomy, Goldblatt 2-kidney hypertension, sodium depletion.

Introduction

Sodium retention has a well-established role in hypertension associated with advanced renal failure and after bilateral nephrectomy (Brown, Düsterdieck, Fraser, Lever, Robertson, Tree & Weir, 1971; Ledingham, 1971). However, in hypertension induced by renal ischaemia, the role of sodium retention is more complicated. When renal artery constriction is combined with contralateral nephrectomy (Goldblatt 1-kidney hypertension), sodium retention plays a partial role in blood pressure elevation (Swales, Thurston, Queiroz & Medina, 1972; Gavras, Brunner, Vaughan & Laragh, 1973; Liard, Cowley, McCaa, McCaa & Guyton, 1974). When the opposite kidney is left undisturbed during renal artery clipping (Goldblatt 2-kidney hypertension) an initial phase of sodium retention has been described (Möhring, Möhring, Naumann, Philippi, Homay, Orth, Dauda, Kazda & Gross, 1975; Leenen, Scheeren, Omylanowski, Elema, Van der Wal & de Jong, 1975), but sodium balance becomes negative as high blood pressures are sustained (Möhring et al., 1975; Swales et al., 1972; Leenen et al., 1975). Although one group found that dietary sodium restriction prevented hypertension in this model (Miksche, Miksche & Gross, 1970) we could not confirm it (Thurston & Swales, 1976).

Studies using infusions of an angiotensin antagonist indicate a major role for the renin–angiotensin system in short-term Goldblatt 2-kidney hypertension (Pals, Masucci, Denning, Sipos & Fessler, 1971), but normal blood pressures have not been achieved (McDonald, Boyd & Peart, 1975).

The present study was designed to determine whether the failure to obtain a complete response to the antagonist was due to sodium retention: we have therefore measured the response to the angiotensin antagonist and to bilateral nephrectomy of rats with Goldblatt 2-kidney hypertension after dietary sodium depletion.

Methods

Female white Wistar rats weighing 150–240 g were used. Hypertension was produced by placing a silver clip (0.2 mm internal diameter) on the left renal artery under ether anaesthesia, with the opposite kidney undisturbed. The rats were weighed and their blood pressures measured by the indirect photoelectric method (Swales & Tange, 1970) before operation and twice weekly afterwards.

Group 1 (normal diet: n = 8)

After surgery the rats received normal rat chow.
containing 0.116 mmol of sodium/g and 0.22 mmol of potassium/g, with free access to tap water. When sustained hypertension (blood pressure > 160 mmHg) had been present for 1–2 weeks the animals were prepared for infusion with the angiotensin II antagonist Sar¹-Ala⁸-angiotensin II. The rats were anaesthetized with intraperitoneal sodium pentobarbitone (5 mg/100 g body weight) and polythene catheters inserted into the carotid artery and jugular vein. Direct blood pressure was monitored using a Statham transducer and recorded by a Grass polygraph recorder. When a steady base-line pressure was obtained, the antagonist was infused at a rate of 10 pmol/min for 5–10 min. Total blockade of the renin–angiotensin system was confirmed by intravenous injection of 73 pmol of angiotensin II (Hypertensin Ciba) at the end of the infusion.

Group 2 (normal diet–bilateral nephrectomy: n = 9)

These rats received the same dietary regimen as the rats in group 1. When hypertension developed they were subjected to bilateral nephrectomy under ether anaesthesia and then allowed to recover. After operation they were given tap water but not food. Six hours after nephrectomy they were anaesthetized with pentobarbitone and the cannulation procedure as described for group 1 was carried out.

Group 3 (low salt diet: n = 8)

These animals received a low salt diet containing 0.004 mmol of sodium/g and 0.211 mmol of potassium/g, and deionized water for 3 days before and then after renal artery constriction. When sustained hypertension developed the antagonist was infused according to the protocol for group 1.

Group 4 (low salt diet–bilateral nephrectomy: n = 8)

These rats were given the same dietary regimen as the animals in group 3 but when a steady level of hypertension was obtained, bilateral nephrectomy was performed under ether anaesthesia. Six hours after operation they were re-anaesthetized with pentobarbitone and a direct arterial blood pressure was obtained.

All results are shown as mean value ± SEM. The Student’s t-test was employed in the statistical analysis of the data.

Results

Group 1. The mean initial blood pressure was 175.1 mmHg (SEM 9.7) and the antagonist produced a significant fall to 127.8 mmHg (SEM 18.5). Four out of the eight animals remained hypertensive during the infusion.

Group 2. Before bilateral nephrectomy these animals had similar blood pressures to those in group 1. Six hours after nephrectomy the mean direct arterial pressure was still elevated at 140.4 mmHg (SEM 11.1).

Group 3. Hypertension developed rapidly in these animals receiving low salt diet. Infusions of the antagonist produced a significant fall in arterial pressure from 171.9 mmHg (SEM 10.7) to 135.3 mmHg (SEM 13.2) but normal levels were not achieved and five animals were still hypertensive.

Group 4. Six hours after bilateral nephrectomy, the eight animals receiving low salt diet had a direct arterial blood pressure of 129.8 mmHg (SEM 8.5), which was not significantly different from the level during antagonist infusions in group 3 (P > 0.5). Three out of the eight animals remained hypertensive after bilateral nephrectomy.

Discussion

These experiments confirm a major role for the renin–angiotensin system in the development of Goldblatt 2-kidney hypertension. Many studies have demonstrated a marked reduction of blood pressure using an angiotensin II antagonist (Sar¹-Ala⁸-angiotensin II) (Pals et al., 1971; Brunner, Kirshman, Sealey & Laragh, 1971; Thurston & Swales, 1974) in the early phase of hypertension, but the response to this agent is variable (McDonald et al., 1975) and does not in general lower the blood pressure to normal levels. Leenen & de Jong (1975) suggested that sodium retention might maintain blood pressure in the presence of angiotensin blockade. However, in this present study prior salt depletion failed to potentiate the depressor action of the antagonist.

In longer standing (i.e. 3–6 months of hypertension) Goldblatt 2-kidney hypertension, the antagonist produces only a small fall in blood pressure (Thurston & Swales, 1974) and although sodium depletion enhances its action, again the blood pressure remains well above normal levels (Gavras, Brunner, Thurston & Laragh, 1975). Therefore sodium retention appears to be of importance in long-standing hypertension but plays no
part in the early phase of Goldblatt 2-kidney hypertension, and an alternative factor must be postulated.

It is possible that the rapid rise in plasma renin and angiotensin II, which is associated with the administration of the antagonist (Bing & Nielsen, 1973), may oppose its action but this would seem unlikely because total blockade to the pressor action of a test dose of angiotensin II could be demonstrated during the infusion. Bing & Nielsen (1973) suggested that the residual hypertension may represent a partial agonist action. On the other hand, 6 h after bilateral nephrectomy the blood pressure was almost identical with that obtained after antagonist infusion, indicating mechanisms other than renin hypersecretion for the persistent hypertension. When the ischaemic kidney is removed from these animals blood pressure falls to normal after 24 h (McDonald et al., 1975; Thurston & Swales, 1976). Thus a reversible renal mechanism distinct from renin secretion and sodium retention may provide the explanation for these findings.

References


