Chemical renal medullectomy; effect upon reversal of two-kidney, one-clip hypertension in the rat

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Summary

1. Chemical renal medullectomy was produced in rats by injection of 2-bromoethylamine hydrobromide. Plasma creatinine and blood pressure were unchanged although urine volume was increased fourfold.

2. Left renal artery constriction resulted in similar degrees of hypertension in both intact and medullectomized rats. This was associated with a significantly smaller rise in plasma renin concentration in the latter.

3. Blood pressure in conscious intact hypertensive rats became normal within 24 h of unclipping whereas blood pressure of medullectomized rats remained significantly elevated.

4. The presence of an intact renal medulla is essential to the complete reversal of two-kidney, one-clip hypertension in the rat. This may reflect the loss of a medullary vasodepressor system.

Key words: 2-bromoethylamine hydrobromide, experimental hypertension, medullectomy.

Introduction

The maintenance of hypertension in the two-kidney, one-clip model in the rat and its rapid reversal after unclipping remain unexplained. Initially high plasma renin levels fall progressively with duration of hypertension and renin-angiotensin blockade results in only partial correction [1]. Sodium balance is negative during the development of hypertension [2], and probably remains so. Unclipping even after several months of hypertension is associated with sodium retention [3]. In a recent study blood pressure fell after unclipping to normal levels within 24 h, before reversal of vascular hypertrophy could have occurred [4]. These data show that neither renin hypersecretion nor sodium retention nor vascular hypertrophy is wholly responsible for the maintenance of hypertension, neither is correction of these changes central to normalization of blood pressure after unclipping.

A number of experiments have shown that the renal medulla has vasodepressor properties [5, 6]. We have therefore studied the effect of chemical medullectomy induced by 2-bromoethylamine hydrobromide [7] on the reversal of two-kidney one-clip hypertension in the rat.

Methods

Female Wistar rats (160–200 g), fed on standard rat show (0.166 mmol of sodium/g) and tap water, were used throughout. All operations, injections, blood sampling and indirect blood pressure measurements [8] were carried out under ether anaesthesia. Bromoethylamine hydrobromide (0.2 g/kg; Aldrich Chemical Co. Ltd, U.K.), as a solution containing 10 g/100 ml in isotonic sodium chloride solution (0.9 g/100 ml) was injected into a jugular vein. Two weeks later after measurement of 24 h urine volume and indirect blood pressure, a silver clip (0.2 mm gap) was placed on the left renal artery; the right kidney was not disturbed. A control group of rats not injected with bromoethylamine was clipped in a similar manner. After 2–4 weeks blood pressure was remeasured and hypertensive animals (>150 mmHg) were selected for study.

A polythene catheter was placed in the left carotid artery, exteriorized between the scapulae and protected by a light, flexible, counterbalanced metal tube, attached to a Statham P23 gb transducer and Grass recorder. On recovery
from the anaesthetic the animals were placed in a plastic container (area 30 cm x 30 cm) with food and water and direct arterial blood pressure was monitored continuously. Patency of the arterial line was maintained by a slow infusion of glucose (5 g/100 ml) containing heparin (5 i.u./ml) at a rate of 0.25 ml/h.

The following day the clip on the left renal artery was exposed through the same loin incision, cleaned and removed. In some control hypertensive rats the clip was exposed but not removed to assess the effect of anaesthesia (sham operation). Direct blood pressure records were continued for a further 24 h. The animals were then killed and the kidneys examined to determine the damage to the renal medulla and cortex.

Plasma renin concentration and creatinine were measured by radioimmunoassay [1] and a spectrophotometric method [9] respectively on blood samples taken before clipping and before cannulation.

Statistical analysis was by paired and unpaired Student's t-tests.

Results

Fourteen days after the injection of 2-bromoethylamine hydrobromide indirect blood pressure was 105 ± 3.2 mmHg (normal 106 ± 3.4; mean ± SEM) and plasma creatinine was 84 ± 12 μmol/l (normal 73 ± 14). These are not significantly different from normal. On the other hand urine volume was markedly increased (38.4 ± 2.7 ml/day, normal 9.1 ± 2.1; P < 0.01) and plasma renin concentration had doubled (91.1 ± 14.6 pmol of angiotensin I h⁻¹ ml⁻¹, normal 48.3 ± 8.6; P < 0.01).

Left renal artery constriction resulted in similar degrees of hypertension. Direct blood pressures before unclipping were 179 ± 4.4 mmHg in medullectomized rats and 183 ± 8.7 mmHg in controls. Mean plasma creatinine had not risen significantly in either group (medullectomized 96 ± 20 and controls 111 ± 33 μmol/l). Plasma renin concentration had risen to 418 ± 104 pmol of ANG I h⁻¹ ml⁻¹ in intact rats (P < 0.01) and was significantly greater than in medullectomized rats (112 ± 22; P < 0.01). However, the plasma renin concentration (PRC) in the latter group was still significantly greater than in normals before clipping (P < 0.01), although not significantly higher than in medullectomized rats before clipping (P > 0.1).

Direct blood pressure (Fig. 1) in hypertensive sham-operated control rats rapidly returned to hypertensive levels on recovery from the anaes-

![Fig. 1. Changes in direct blood pressure (mmHg) after unclipping in medullectomized (A--A) and intact (■—■), and in sham-operated (○—○) two-kidney, one-clip hypertensive rats.](image-url)
thetic and at 24 h was not significantly different from pre-operative values (173 ± 4.3 vs 181 ± 9.0 mmHg respectively; n = 8, P > 0.1). Unclipped rats with intact renal medullas showed a small rise in blood pressure postoperatively, which fell to normal levels by 24 h (114 ± 5.5 mmHg; n = 11, P < 0.001, compared with pre-unclipping). Hypertensive medullectomized rats showed a similar fall in blood pressure during the unclipping procedure but on recovery from the anaesthetic blood pressure rose to significantly higher levels than that of control unclipped animals (166 ± 7.9 vs 139 ± 5.4 mmHg respectively; P < 0.01) and remained significantly higher than this group throughout the period of study (144 ± 5.2 mmHg at 24 h; P < 0.01 compared with unclipped controls). However, the blood pressure in the medullectomized rats did not return to pre-operative levels and was significantly lower than that of the sham-operated group at 24 h (P < 0.01).

Macroscopic examination of the kidneys showed loss of the renal papilla in all rats treated with bromoethylamine. Histologically in these same kidneys the tubules were dilated with interstitial cellular infiltrates but the cortices and glomeruli appeared the same as those of kidneys from intact controls.

Discussion

We have previously demonstrated that complete reversal of two-kidney, one-clip hypertension in the rat cannot be achieved by renin–angiotensin blockade, whereas unclipping is effective even after several months of hypertension [1]. This fall in blood pressure was not associated with a natriuresis or dependent on reversal of vascular changes or renin [2, 3]. Therefore some alternative mechanism must be involved.

Recently there has been interest in possible vasodepressor properties of the renal medulla [5, 6]. Bromoethylamine hydrobromide produces selective necrosis of the renal medulla [7], and the resulting polyuria is associated with only minor changes in renal function [10]. Chemical medullectomy has little effect on blood pressure in normal and two-kidney, one-clip hypertensive rats [11]. In the present study rats pretreated with bromoethylamine showed no change in blood pressure or plasma creatinine although urine volume was increased fourfold. Subsequent clipping of the left renal artery resulted in a degree of hypertension comparable with that in clipped control animals with intact renal medullas. Mean plasma creatinine had risen slightly in both groups although in the majority of hypertensive rats it remained normal. The rise in plasma renin concentration after clipping was significantly greater in the rats with intact renal medullas. However, even in medullectomized rats the PRC was significantly higher than in normals.

The response in blood pressure to removal of the constricting clip on the left renal artery was considerably modified by the absence of the renal medulla. During the anaesthetic the blood pressure fell to similar levels in all groups of rats; however, postoperatively blood pressure of unclipped medullectomized rats recovered to a greater extent than that of unclipped intact rats and was significantly higher from 3 h to the end of the study (24 h). Unclipping in medullectomized rats was not totally ineffective and blood pressure was significantly lower in this group than both pre-operative values and blood pressure in sham-operated intact hypertensive rats at 24 h.

An intact renal medulla appears to be essential to complete reversal of two-kidney, one-clip hypertension in the rat. This is similar to the findings in the one-kidney, one-clip model, where surgical medullectomy delays the final response to unclipping. This, however, can be corrected by transplantation of a normal renal medulla into these animals [12]. The renal medulla is capable of prostaglandin synthesis although the use of prostaglandin synthetase inhibitors does not affect either the development or reversal of renal hypertension [13, 14]. Muirhead [15] has described the partial isolation and synthesis of a non-prostaglandin antihypertensive lipid from the renal medulla of rats and the present findings are consistent with the hypothesis that this material has a physiological role.

Chemical medullectomy provides a useful model for studying the possible changes in a reno-medullary vasodepressor system that occur during and after reversal of two-kidney, one-clip hypertension in the rat.

References


