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CENTRAL AND PERIPHERAL NORADRENALINE IN THE TWO KIDNEY MODEL OF RENOVASCULAR HYPERTENSION IN THE RAT

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1 Plasma noradrenaline concentrations were similar in rats following unilateral renal arterial constriction (two kidney Goldblatt model) and in sham-operated control rats.

2 The development of hypertension was not affected by pretreatment with intracisternal injections of 6-hydroxydopamine.

3 These data suggest that sympathetic mechanisms do not contribute to the development of hypertension in this model.

Introduction

The importance of central noradrenergic neurones has been established in several models of experimental hypertension (Haeusler, Finch & Thoenen, 1972; Chalmers, Dollery, Lewis & Reid, 1974; Lewis, Dargie & Dollery, 1975). In the model of renovascular hypertension in the rat in which the renal arterial constriction is accompanied by contralateral nephrectomy (one kidney Goldblatt), pretreatment with intracisternal 6-hydroxydopamine (6-OHDA), which causes a long-lasting depletion of central noradrenergic neurones, has been shown to prevent the development of hypertension (Haeusler *et al.*, 1972; Dargie, Franklin & Reid, 1976). Pretreatment with intracisternal 6-OHDA has also prevented the increase in plasma noradrenaline (NA) concentrations which accompanies the increase in blood pressure (Dargie *et al.*, 1976).

In the model of renovascular hypertension in which renal arterial constriction only is performed, the other kidney being left intact (two kidney Goldblatt), the hypertension is primarily dependent on increased activity of the renin angiotensin system (Brunner, Gavras & Laragh, 1974).

In the present study we have assessed the contribution of the sympathetic nervous system to the hypertension in the two kidney model by measuring plasma NA concentrations at various times following renal arterial constriction and have examined the effect of pretreatment with intracisternal 6-OHDA both on the development of hypertension and on plasma NA concentrations.

Methods

Male Wistar rats weighing 200 g had a silver clip 0.009 inch wide placed over the left renal artery while control rats underwent a sham operative procedure involving placement of a broad non-constricting clip over the left renal artery. Blood pressure was measured by tail plethysmography using a programmed electrosphygmomanometer and pneumatic pulse transducer (Narco Biosystems Inc.). At 24 h 7, 24 and 28 days after operation, groups of 6 to 8 renal arterial clip rats together with their sham-operated controls were killed by decapitation 4 to 6 h after the blood pressure measurement (see Roizen, Weise, Moss & Kopin, 1975). The first 1 ml of 'arterialized' blood from the trunk was collected in ice-cold heparinized tubes for estimation of NA by the method of Henry, Starman, Johnson & Williams (1975).

Two groups of 20 rats were pretreated 14 days before renal arterial manipulation with either two intracisternal injections of 6-OHDA 200 μg or an identical volume (20 μl) of ascorbate saline vehicle the interval between injections being 48 hours. Blood pressure was measured by tail plethysmography at 1 and 7 days following renal arterial manipulation. Blood pressure and plasma NA concentrations were measured in two further groups of rats pretreated with either intracisternal 6-OHDA or vehicle at 7 days following renal arterial manipulation.

Results

Blood pressure and plasma noradrenaline concentration

In the first series of experiments mean systolic blood pressure was significantly elevated in the renal arterial clip group at 24 h, 7, 14 and 28 days reaching a maximum of 161 ± 5 mmHg at 7 days following renal

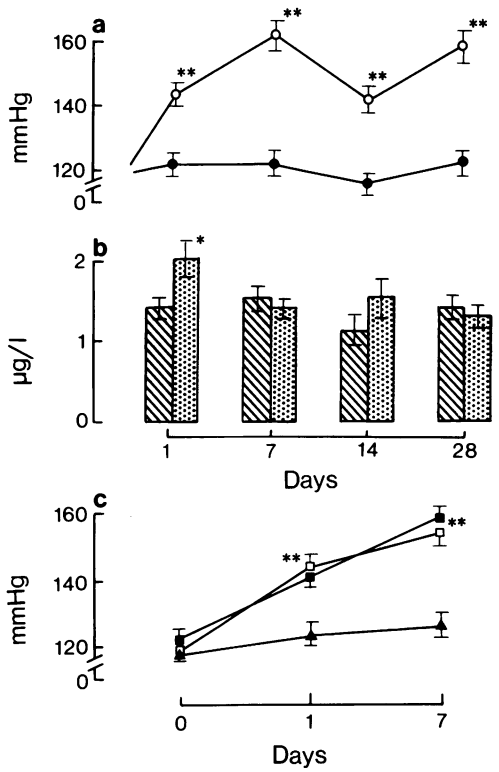

Figure 1 (a) Systolic blood pressure (mean) in renal arterial clip rats (O) and sham operated controls (●) at 1, 7, 14 and 28 days after renal manipulation. Vertical lines show s.e. mean. (b) Plasma noradrenaline concentrations (mean) in renal arterial clip rats (hatched columns) and sham-operated controls (stippled columns) at 1, 7, 14 and 28 days after renal manipulation. Vertical lines show s.e. mean. (c) Systolic blood pressures (mean) in renal arterial clip rats pretreated with intracisternal 6-hydroxydopamine (■) or vehicle (□) at 1 and 7 days after renal arterial manipulation and control unoperated rats (▲). Vertical lines show s.e. mean. * $P<0.05$; ** $P<0.001$ (Student's t test).

arterial manipulation ($P<0.01$). The sham-operated group did not become hypertensive at any time during the experiment (Figure 1a). At 7 days when the blood pressure was highest, plasma NA in the renal arterial clip group was 1.50 ± 0.20 µg/l which was not significantly different from the value of 1.52 ± 0.18 µg/l obtained in the sham-operated control group at the same time. Although at 24 h after operation plasma NA was slightly but significantly higher in the sham-operated group than in the renal arterial clip group, at no time was the plasma NA level significantly greater in the renal clip group than in the sham-operated controls (Figure 1b).

Effect of intracisternal 6-hydroxydopamine

Mean systolic blood pressure in the first group of renal arterial clip rats pretreated with intracisternal 6-OHDA was not significantly different from renal arterial clip rats pretreated with intracisternal vehicle at either 24 h or 7 days following operation, values being 144 ± 5.0 mmHg and 146 ± 6 mmHg respectively at 24 h and 159 ± 5 mmHg and 150 ± 5 mmHg respectively at 7 days. All these values were significantly greater than in sham-operated rats whose blood pressures were 119 ± 4 mmHg and 129 ± 4 mmHg at 24 h and 7 days respectively following operation ($P<0.001$) (Figure 1c). Mean systolic blood pressure in the further group of renal arterial clip rats pretreated with intracisternal 6-OHDA was not significantly different from renal arterial clip rats pretreated with intracisternal vehicle, values being 129 ± 4 mmHg and 136 ± 3 mmHg respectively. Both these values were significantly higher than their sham-operated controls whose pressures were 113 ± 8 mmHg and 116 ± 3 mmHg ($P<0.001$). Plasma NA concentrations in both renal arterial clip groups were not significantly different from sham-operated animals pretreated with intracisternal vehicle, values being 1.58 ± 0.44, 1.30 ± 0.22 and 1.55 ± 0.34 µg/l respectively. The only difference was that plasma NA in the sham-operated rats pretreated with intracisternal 6-OHDA was lower than the other three operated groups at 0.81 ± 0.25 µg/l ($P<0.05$). However, this value was not significantly different from that of a non-operated normotensive control group killed at the same time in which plasma NA was 0.97 ± 0.25 µg/litre.

Discussion

In this study we have shown that the development of hypertension after renal arterial constriction with an intact contralateral kidney (two kidney Goldblatt) is not associated with an increase in plasma NA levels, nor is the hypertension modified by pretreatment with intracisternal 6-OHDA which depletes central noradrenergic neurones. There have been few studies of sympathetic function in the two kidney Goldblatt model but in one recent study neonatal sympathectomy had no effect on the development of hypertension in this model (Provoost, Bohus & de Jong, 1976) confirming the lack of dependence of the raised blood pressure on sympathetic mechanisms. These data contrast sharply with previous experience with the one kidney Goldblatt model in the rat in which an increase in plasma NA accompanies the development of hypertension and in which pretreatment with intracisternal 6-OHDA prevents not only the development of hypertension but also the increase in plasma NA concentrations (Dargie *et al.*,

1976). Similar data have been obtained in the deoxycorticosterone acetate (DOCA) salt model in the rat (Reid, Zivin & Kopin, 1975) and increased plasma NA concentrations have also been described in spontaneous hypertension in the rat (Grobecker, Roizen, Weise, Saavedra & Kopin, 1976). Pretreatment with intracisternal 6-OHDA prevents hypertension not only in the DOCA salt and the one kidney Goldblatt models but also in the perinephritis model in the rabbit in which bilateral cellophane wrapping of the kidneys results in interstitial nephritis. This suggests that in these models the development of hypertension results from a centrally mediated increase in sympathetic activity.

In our previous studies with the one kidney Goldblatt model, plasma NA was high in both the renal arterial clip and sham-operated groups at 24 h after the operative procedure (Dargie *et al.*, 1976). This was carried out under ether anaesthesia and we attributed the elevation of plasma NA at this stage to anaesthesia and operative stress, and the high plasma NA in the sham-operated group in the present study at 24 h could be related to similar mechanisms. The lower level in the renal arterial clip group cannot be explained at present and further studies will be required to determine its physiological significance, if any.

In the two kidney Goldblatt model, dependence on the renin angiotensin system has been suggested by increased plasma levels of renin and angiotensin II (Koletsky, Paulico & Rivera-Velez, 1971) and more recently confirmed by the use of specific angiotensin II antagonists (Brunner *et al.*, 1974). Angiotensin II can stimulate sympathetic activity centrally via an action on the area postrema in the mid brain (Joy & Lowe, 1969) and it is possible that any resulting increase in sympathetic activity might contribute to the development and maintenance of hypertension in the two kidney model. However, the absence of any increase of plasma NA concentration in the renal arterial clip animals in the present study and the lack of effect on the development of hypertension of depletion of central noradrenergic neurones by intracisternal 6-OHDA indicate that the central and peripheral sympathetic nervous system do not play a major role in the development of hypertension in the two kidney Goldblatt model of experimental hypertension in the rat.

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