Enhanced hypothalamic noradrenaline biosynthesis in Goldblatt I renovascular hypertension

VINCENT DEQUATTRO, IVAR EIDE, MARK R. MYERS, KARI EIDE, RAINER KOLLOCH AND HOWARD WHIGHAM

Hypertension Service, Department of Medicine, University of Southern California School of Medicine, and Department of Applied Physiology, White Memorial Medical Center, Los Angeles, California, U.S.A.

Abstract

1. Hypertension was induced in rats by renal artery clip with the contralateral kidney removed (Goldblatt I) or left intact (Goldblatt II).
2. Plasma noradrenaline was increased 62% in the Goldblatt I animals after 3 weeks.
3. Hypothalamic tyrosine hydroxylase and dopamine β-hydroxylase activities, and the concentration of noradrenaline were increased in the Goldblatt I animals after 3 weeks.
4. Enhanced hypothalamic noradrenaline synthesis may be a pathogenic factor in Goldblatt I renovascular hypertension.

Key words: dopamine-β-hydroxylase, plasma noradrenaline, renovascular hypertension, tyrosine hydroxylase.

Introduction

Recent findings in rats with Goldblatt I renovascular hypertension suggest that increased peripheral sympathetic nerve activity is a pathogenic factor in the development and maintenance of the hypertension (Reid, Dargie, Franklin & Fraser, 1976; Dargie, Franklin & Reid, 1976). This is a report of our findings in plasma and hypothalamus of both the one-kidney and two-kidney models of renovascular hypertension in the rat. Enhanced noradrenaline synthesis in the hypothalamus leading to increased central and peripheral sympathetic tone are important factors in the pathogenesis of Goldblatt I hypertension.

Methods

Male Wistar rats (weights 214–276 g) were divided into 3 groups: 1, Goldblatt I (1K); 20 animals had a silver clip of 0.22 mm internal diam. placed on the left renal artery 3 weeks after right nephrectomy. 2, Goldblatt I1 (2K); 17 rats underwent clipping of the left renal artery without contralateral nephrectomy. 3, Sham-operated animals; 10 rats underwent laparotomy with exposure of the left renal artery. All animals were on water ad lib and standard rat chow diet.

While under light ether anaesthesia, a cannula was placed first in the left femoral artery 1 day pre-operatively and again in the right femoral artery 21 days postoperatively to obtain mean arterial blood pressure, and a 1-0 ml blood sample. Blood pressures and samples were taken in the awake resting animal. Blood was stored at −20°C and assayed for noradrenaline and adrenaline by a radioenzymic method (Peuler & Johnson, 1977). Systolic blood pressure was measured from the right hind paw 8, 5 and 2 days pre-operatively and on days 13, 17 and 20 postoperatively by the cuff photoelectric method (Metro Scientific Inc.). Rats were decapitated at 21 days; the brain was separated into brain stem, hypothalamus and forebrain (Glowinski & Iversen, 1966). Tissues were stored on solid CO2 and assayed for noradrenaline (Peuler & Johnson, 1977), tyrosine hydroxylase (Nagatsu, Levitt & Udenfriend, 1964), and dopamine-β-hydroxylase (Nagatsu & Udenfriend, 1972). Paired or two-sample Student's t-tests were performed.
TABLE 1. Blood pressures, plasma and hypothalamic noradrenaline concentrations, and activities of noradrenaline-synthesizing enzymes in the hypothalamus of rats with Goldblatt I and II hypertension

n.s. = not significant. Numbers in parentheses indicate the numbers of animals studied.

<table>
<thead>
<tr>
<th>Group</th>
<th>Blood pressures</th>
<th>Noradrenaline</th>
<th>Enzymes (nmol h⁻¹g⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Indirect</td>
<td>Direct</td>
<td>Plasma ang/l</td>
</tr>
<tr>
<td></td>
<td>systolic arterial pressure</td>
<td>mean arterial pressure</td>
<td>Plasma Hypothalamus (μg/g)</td>
</tr>
<tr>
<td>1K Goldblatt</td>
<td>199 ± 4 (14)</td>
<td>143 ± 5 (16)</td>
<td>401 ± 66 (13)</td>
</tr>
<tr>
<td>2K Goldblatt</td>
<td>186 ± 8 (17)</td>
<td>130 ± 4 (15)</td>
<td>254 ± 61 (9)</td>
</tr>
<tr>
<td>Sham-operated</td>
<td>131 ± 4 (10)</td>
<td>100 ± 5 (10)</td>
<td>226 ± 57 (7)</td>
</tr>
</tbody>
</table>

Differences P <

1K vs sham      0.001 0.001 0.05 0.001 0.05 0.025
1K vs 2K        n.s. 0.05  n.s. 0.001 n.s.  n.s.
2K vs sham      0.001 0.001  n.s. n.s. n.s. n.s.

Results

Systolic blood pressure and mean arterial pressure of both groups of rats with clips applied to the renal artery were increased after 3 weeks (Table 1). The magnitude of blood pressure elevation was greater in the 1K model and there was a 15% mortality rate in this model. Blood pressures of sham-operated animals increased slightly but not significantly at 3 weeks. Mean arterial pressure measured directly was closely related to the indirect systolic blood pressure (r = 0.70, P < 0.001). The mean plasma noradrenaline concentration of the 1K animals was increased 62% at 21 days but was unchanged in the 2K and sham-operated rats. Plasma adrenaline was not changed by the surgical intervention of any of the groups at 21 days.

The activities of the tissue enzymes and concentration of noradrenaline were greater in hypothalamus than in brain stem and forebrain. Hypothalamic tyrosine hydroxylase and dopamine-β-hydroxylase activities of the 1K animals were 48% and 34%, and 28% and 39% greater than those of the 2K and sham-operated animals respectively (Table 1). The mean noradrenaline content of hypothalamus in the 1K animals was 66% greater than those of the 2K and sham-operated rats.

Discussion

Systolic blood pressure, measured indirectly, and the mean arterial pressure, measured directly from the femoral arteries, verified the development of renovascular hypertension in both the 1K and 2K animals. The increased plasma noradrenaline in 1K renovascular hypertension is evidence of increased peripheral sympathetic tone. Increased sympathetic tone has been shown to be associated with hypertension in both man and laboratory animals (DeQuattro & Chan, 1972; DeChamplain, Farley, Cousineau & van Ameringen, 1976). Dargie et al. (1976) have reported a twofold increase in plasma noradrenaline in 1K hypertensive rats. Increased cardiac noradrenaline turnover has previously been found in these animals (Henning, 1969).

The increased noradrenaline in the hypothalamus of 1K animals implicates it as the possible central site of increased sympathetic tone. Dargie, Franklin & Reid (1977) found that intracisternal pretreatment with 6-hydroxydopamine prevented both the rise in blood pressure and plasma catecholamines. On the other hand, Petty & Reid (1977) found a reduction of noradrenaline in hypothalamus and brain stem at 3 days and no change at 7 days. At 4 weeks, similar to the time used in our study, there were changes in only two areas: a 61% reduction in the parahypoglossal nucleus of brain stem and a 167% increase in the cerebellar cortex. The increased activities of both biosynthetic enzymes in the 1K rats of this study indicate enhanced noradrenaline synthesis and release in the hypothalamus. Although these are gross changes and the specific areas responsible remain to be localized, an important role for the sympathetic nervous system in the pathogenesis of the renovascular hypertension is likely.

The mechanisms responsible for stimulation of the central and peripheral sympathetic nervous system have not been identified. Plasma renin
activity is elevated in the 2K, but not the 1K model of renovascular hypertension (Gavras, Brunner, Vaughan & Laragh, 1973). Saralasin, an angiotensin II β-adrenoceptor blocker, lowers blood pressure in the sodium replete 2K model, but not the 1K model (Gavras et al., 1973). Perhaps a lower concentration of angiotensin II or a transient elevation serves to stimulate hypothalamic centres controlling noradrenaline synthesis whereas the higher concentration found in the Goldblatt II rats inhibit or neutralize these effects.

The findings of this study serve to further implicate the sympathetic nervous system in the pathogenesis of renovascular hypertension. The changes in noradrenergic function are specific to the Goldblatt I model of hypertension and do not appear to be a consequence of the hypertension. Central noradrenergic pathways of the hypothalamus appear to be important in the genesis of 1K renovascular hypertension.

Acknowledgments

We gratefully acknowledge the technical assistance of Mr Dantje Meijer and thank Ms Grace Fung for the preparation of the manuscript. This work was supported in part by a Fogarty Fellowship Award to Dr Ivar Eide, Institute Experimental Medical Research, Ullevaal Hospital, Oslo, Norway. Dr Rainer E. Kolloch was supported by the Deutsche Forschungsgemeinschaft.