Systemic and regional haemodynamics in anterior hypothalamic hypertension in spontaneously hypertensive and Wistar–Kyoto rats

D. H. SUAREZ, BARBARA L. PEGRAM AND E. D. FROHLICH

Salmen Family Hypertension Research Laboratory, Alton Ochsner Medical Foundation, New Orleans, Louisiana, U.S.A.

Summary

1. Systemic and regional haemodynamics were determined in conscious Wistar–Kyoto and spontaneously hypertensive rats with the radioactive microsphere technique after sham lesion or bilateral electrolytic lesion of the nuclei of the anterior hypothalamus.

2. Anterior hypothalamic lesions produced an increase in blood pressure, heart rate and cardiac output.

3. In the rats with lesions there were changes in regional haemodynamics: heart and skeletal muscle flow increased; renal, skin and splanchnic flow decreased.

4. The haemodynamic consequences of ablation of the anterior hypothalamus were similar in both normotensive Wistar–Kyoto and spontaneously hypertensive rats. The haemodynamic pattern resembles that seen during fighting and exercise.

Key words: anterior hypothalamus, blood flow, haemodynamics, hypertension, spontaneously hypertensive rats, Wistar–Kyoto rats.

Introduction

In spontaneously hypertensive rats (SH rats), separation of the connection between the hypothalamus and mesencephalon produces a more pronounced fall in arterial pressure than in normotensive control rats (Yamori & Okamoto, 1969). Conversely, electrical stimulation of the posterior hypothalamus produces a greater pressor response in conscious SH rats (Bunag, Eferakeya & Langdon, 1975). Thus several studies have implicated hypothalamic dysfunction in SH rats. Ablation of the anterior hypothalamus in rats increases arterial pressure, associated with behavioural changes (Nathan & Reis, 1975). In the present study we have investigated the systemic and regional haemodynamic effects of bilateral anterior hypothalamic lesions in Wistar–Kyoto (WK) rats and spontaneously hypertensive SH rats.

Methods

Twenty-six-week old SH and WK rats were used in these experiments. Under light ether anaesthesia, cannulae (PE 50) were inserted into the left ventricle of these rats through the right carotid artery and into the abdominal aorta through the right femoral artery; locations of catheter tips were confirmed by pressure tracings. All cannulae were exteriorized through a subcutaneous tunnel at a point midway between the scapulae and connected by Statham P23 ID strain-gauge transducers to a Grass recorder (model 79D).

After the above cannulations the rat was placed in a stereotaxic apparatus (David Kopf Instruments) and the tooth bar was positioned 2.5 mm below the level of the interaural line. The tip of the stainless-steel monopolar electrode (0.3 mm) was positioned 7.8 mm anterior to the interaural line and 0.6 mm left of the midline and it was then lowered to a depth of 1.6 mm above the interaural plane. Lesions were then made by passing a constant anodal current (1.5 mA for 15 s duration) through an electrode which had been insulated (Epoxilite 6001) except for an exposed bevelled tip of 0.5 mm. The cathode was a clip
that had been attached to the adjacent temporalis muscle. The second lesion was placed at a homologous point on the contralateral side of the brain. In sham-lesion rats the electrode was positioned with the same co-ordinates, but no current was passed. After the lesion was placed, the rats were put in a small plastic chamber.

Systemic and regional haemodynamics were measured in the conscious rat 1.5 h after placement of the electrode (sham) or the bilateral lesions and after the rats had recovered fully from the anaesthesia. Radioactive microspheres (3M Company, St Paul, Minn., U.S.A.) labelled with $^{85}$Sr or $^{51}$Cr were injected into the left ventricle and flushed with 0.4 ml of sodium chloride solution (154 mmol/l: saline) to determine simultaneously cardiac output (by the reference sample method) and regional blood flows (by previously reported techniques: Tsuchiya, Ferrone, Walsh & Frohlich, 1978; Ferrone, Walsh, Tsuchiya & Frohlich, 1979). In brief, 0.05 ml of carbonized radiomicrospheres containing approximately 40 000 spheres (15 μm diameter) were placed in a 5 cm length Silastic tubing (inside diameter 0.040 mm × outside diameter 0.085 mm; Dow Chemical Co. Midland, NJ, U.S.A.). The tubing was capped at both ends and the radioactivity was determined in a Packard Auto-Gamma Scintillation Spectrometer. Immediately before injection into the left ventricle aggregates of the spheres were dispersed ultrasonically and, after injection, residual radioactivity of the catheter was determined.

A reference sample was withdrawn from the femoral arterial catheter into a preweighed heparinized 1 ml syringe at a rate of approximately 1.2 ml/min (sampling rate). Withdrawal began 10 s before microsphere injection and was maintained for 50 s. After the syringe was weighed, the blood that had been withdrawn was placed in a scintillation vial. The syringe was rinsed repeatedly with saline until no radioactivity remained in the syringe. Cardiac output was calculated as follows:

Cardiac output (ml/min) =

\[
\frac{\text{sampling rate (ml/min) \times injected counts (c.p.m.)}}{\text{reference sample counts (c.p.m.)}}
\]

The rats were killed by exsanguination under ether anaesthesia and the organs were removed, weighed and counted for total radioactivity in the deep-well gamma-scintillation counter. The fraction of cardiac output to each organ was calculated from the ratio of radioactivity of each organ to total radioactivity injected. Absolute organ flow (ml/min) could therefore be quantified by multiplying the distribution fraction of cardiac output to each organ by the simultaneously measured cardiac output (reference method). Vascular resistance (index) for that organ was obtained by dividing mean arterial pressure by that organ blood flow (ml/g of tissue). After total brain radioactivity had been determined, the brain was placed in 10% formalin. Localization of brain lesions was confirmed from frozen sections that were cut at 40 μm intervals and mounted on agar-coated glass slides and stained with toluidine blue and basic fuchsin. Students t-test was used to ascertain significant differences. Values were expressed as means ± SEM.

Results

At 1.5 h after placement of the lesions, during which time all rats exhibited hypermotility and increased aggressiveness, haemodynamic changes were measured. Increases in mean arterial pressure (sham 113 ± 3; lesion 138 ± 5 mmHg; P < 0.001), heart rate (sham 376 ± 12; lesion 473 ± 14 beats/min; P < 0.001) and cardiac index (sham 224 ± 14; lesion 282 ± 12 ml min⁻¹ kg⁻¹; P < 0.01), but not in total peripheral resistance index (sham 0.515 ± 0.0030; lesion 0.479 ± 0.029 unit), were found in the normotensive WK rats. Significant increases were found also in mean arterial pressure (sham 165 ± 3; lesion 189 ± 3 mmHg; P < 0.001) and heart rate (sham 422 ± 13; lesion 495 ± 5 beats/min; P < 0.001) in the SH rats but the cardiac index (sham 257 ± 18; lesion 288 ± 17 ml min⁻¹ kg⁻¹ and total peripheral resistance index (sham 0.670 ± 0.052; lesion 0.677 ± 0.045 unit) were not statistically significant. The fractional distribution of cardiac output in SH and WK rats with lesions was decreased to skin (P < 0.001; P < 0.001), kidney (P < 0.001; P < 0.001) and splanchnic organs (P < 0.01; P < 0.001) and increased to muscle (P < 0.001; P < 0.01) respectively. In heart, the fractional flow/g of tissue increased only in the WK rats (P < 0.05), but the absolute blood flow/g of tissue increased significantly in both strains (Table 1).

Discussion

The increased mean arterial pressure produced by bilateral anterior hypothalamic lesions was associated with significant haemodynamic alterations. In WK rats these changes were characterized by an increase in both heart rate and cardiac output. The heart rate in SH rats significantly increased and cardiac output tended
TABLE 1. Regional haemodynamics in sham-lesion control (C) and bilateral anterior hypothalamic lesion (L) conscious normotensive Wistar—Kyoto and spontaneously hypertensive rats

<table>
<thead>
<tr>
<th></th>
<th>Wistar—Kyoto rats</th>
<th>Spontaneously hypertensive rats</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fractional flow (% of cardiac output/g)</td>
<td>Blood flow (ml min(^{-1}) g(^{-1}))</td>
</tr>
<tr>
<td>Skin</td>
<td>C 0.080 ± 0.006</td>
<td>0.068 ± 0.005</td>
</tr>
<tr>
<td></td>
<td>L 0.048 ± 0.003***</td>
<td>0.051 ± 0.005*</td>
</tr>
<tr>
<td>Muscle</td>
<td>C 0.090 ± 0.008</td>
<td>0.078 ± 0.008</td>
</tr>
<tr>
<td></td>
<td>L 0.027 ± 0.025**</td>
<td>0.229 ± 0.031***</td>
</tr>
<tr>
<td>Brain</td>
<td>C 0.868 ± 0.074</td>
<td>0.730 ± 0.039</td>
</tr>
<tr>
<td></td>
<td>L 0.852 ± 0.050</td>
<td>0.903 ± 0.054*</td>
</tr>
<tr>
<td>Heart</td>
<td>C 4.845 ± 0.499</td>
<td>4.286 ± 0.668</td>
</tr>
<tr>
<td></td>
<td>L 6.898 ± 0.450*</td>
<td>7.413 ± 0.659*</td>
</tr>
<tr>
<td>Kidney</td>
<td>C 9.405 ± 0.632</td>
<td>8.231 ± 0.877</td>
</tr>
<tr>
<td></td>
<td>L 4.910 ± 0.496**</td>
<td>5.127 ± 0.374***</td>
</tr>
<tr>
<td>Splanchnic organs</td>
<td>C 0.883 ± 0.045</td>
<td>0.763 ± 0.065</td>
</tr>
<tr>
<td></td>
<td>L 0.546 ± 0.090**</td>
<td>0.552 ± 0.064*</td>
</tr>
</tbody>
</table>

Support Grant RR 05518. This study was performed while D.H.S. was a fellow of the American Heart Association of Louisiana Inc.

References


to increase, although this was not significant. In both WK and SH rats blood flow to skin, kidney and splanchnic organs decreased, whereas flow to heart and skeletal muscle increased. This blood flow distribution differs from that observed in acute arterial hypertension produced by bilateral lesions of the nucleus tractus solitarii (Snyder, Doba & Reis, 1978). Acute nucleus tractus solitarii hypertension resulted in a reduction in flow to skin, skeletal muscle, kidney and splanchnic organs without changes in flow to the heart.

In the present study, the haemodynamic consequences of ablation of the anterior hypothalamus were qualitatively similar in WK and SH rats and are similar to those findings previously reported in normotensive American Wistar rats (Suarez, Pegrarum, Aristimuno & Frohlich, 1979). Thus these findings suggest that the haemodynamic pattern observed in WK and SH rats immediately after anterior hypothalamic lesions resembles that seen during fighting (Adams, Baccelli, Mancia & Zanchetti, 1969) and exercise (Adams, Baccelli, Mancia & Zanchetti, 1971) in cats.

Acknowledgments

This study was supported in part by grants-in-aid from the National Heart, Lung and Blood Institute HL 20542 and Biomedical Research.