Systemic and Regional Hemodynamic Changes Associated with Anterior Hypothalamic Lesions in Conscious Rats

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SUMMARY Systemic and regional hemodynamics were determined with the radioactive microsphere technique either in conscious “sham-lesioned” Wistar rats or after bilateral electrolytic lesions of the nuclei of the anterior hypothalamus. Both mean arterial pressure (111 ± 4 vs 152 ± 3 mm Hg) and heart rate (376 ± 15 vs 504 ± 12 beats/min) were significantly increased 2 hours after lesioning (p < 0.001). Although cardiac output tended to increase, it did not attain statistical significance; therefore this form of neurogenic hypertension is characterized by increased total peripheral resistance. Regional hemodynamics were measured 2 hours after placement of the lesions: skeletal muscle flow increased, renal cutaneous and splanchnic flows decreased, and brain and myocardial flows were preserved. These hemodynamic alterations were associated with significant elevations in plasma norepinephrine and epinephrine levels, and behavioral changes characterized by hypermotility, aggressivity, and irritability, which resembled those seen during fighting and exercise.

(Hypertension 3: 245-249, 1981)

KEY WORDS • hypertension • anterior hypothalamic nuclei • cardiac output • regional blood flow • lesions

A CUTE central neurogenic hypertension can be produced either by lesions of nucleus tractus solitarius or anterior hypothalamic (AH). Bilateral electrolytic lesions of the latter area result in a rapid increase in arterial pressure, heart rate, and motor activity. The increased pressure appears to result from neurally-mediated release of adrenomedullary catecholamine, since it can be prevented by adrenalectomy. In the present study we have determined systemic and regional hemodynamic changes following bilateral AH lesions, to ascertain the contribution of each vascular bed to the increased arterial pressure.

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Supported in part by grants-in-aid from the National Heart, Lung and Blood Institute (HL 20542 and HL 20572) and Biomedical Research Support Grant RR 05518.

This study was performed while Dr. Daniel H. Suarez was a recipient of the following awards: the Ouachita Parish Central Trades and Labor Council and Affiliates, Richard J. Carrere, Hibernia National Bank, and American Heart Association-Louisiana, Inc.

This paper was presented in part at the 52nd Scientific Session of the American Heart Association Meeting, Anaheim, California, November, 1979.

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Received February 12, 1980, revision accepted August 12, 1980.

Methods

Twenty-two male normotensive Wistar rats (West Jersey Biological Supply, Wenonah, New Jersey) weighing between 300 and 400 g were used in these experiments. With the rats under ether anesthesia, canulas (PE 50) were inserted into the left ventricle through the right carotid artery and into the abdominal aorta through the right femoral artery, with confirmation of the location by pressure tracings. All canulas were exteriorized through a subcutaneous tunnel at a point midway between the scapulas and connected to Statham P23 1D strain gauge transducers and a Grass recorder (Model 79D).

Placement of Anterior Hypothalamic Lesion

After the above cannulations were done, the animal 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, 0.6 mm left of the midline, and lowered to a depth of 1.8 mm above the interaural plane. Lesions were then made by passing an anodal constant current (2mA for 30 seconds 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 temporal muscle. The second lesion was placed at a homologous point on the contralateral side of the brain. In sham-lesioned rats, the electrode was positioned using the same coordinates, but no lesioning current was passed. After the lesion was placed, the rats were put in a small plastic chamber (20 × 4 × 5 cm) and allowed to recover from the anesthesia before the systemic and regional hemodynamic alterations were ascertained.

Systemic and Regional Hemodynamics

Systemic and regional hemodynamics were measured in the conscious rat 2 hours after placement of the electrode (sham) or the bilateral lesions after the rats had recovered fully from the anesthesia. Radioactive microspheres (3M Company, St. Paul, Minnesota) labelled with $^{80}$Sr or $^{85}$Cr were injected into the left ventricle and flushed with 0.4 ml saline to simultaneously determine cardiac output (CO) by the reference sample method and regional organ blood flows using previously reported techniques. In brief, 0.05 ml of carbonized radiomicrospheres containing approximately 40,000 spheres (15 ± 5 μ in diameter) was placed in a 5-cm length Silastic tubing (ID 0.040 × OD 0.085, Dow Chemical Company, Midland Park, New Jersey). The tubing was capped at both ends and the radioactivity was determined in a Packard Auto-Gamma Scintillation Spectrometer. Immediately before injection in the left ventricle, aggregates of the spheres were dispersed, 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. Withdrawal began 10 seconds prior to microsphere injection and was maintained for 50 seconds. After weighing the syringe, the blood that had been withdrawn was placed in a scintillation vial. The syringe was rinsed with saline and the saline added to the vial until no radioactivity remained in the syringe. Cardiac output was calculated as follows:

$$\text{CO (ml/min)} = \frac{\text{SR (ml/min) Injected isotope counts (cpm)}}{\text{Reference sample counts (cpm)}}$$

where

$$\text{Sampling rate (SR ml/min)} = \frac{(\text{Change in syringe weight}) (60 \text{ sec/min})}{(\text{Specific gravity of blood}) (50 \text{ sec})}.$$ 

The rats were killed by exsanguination under ether anesthesia, and the organs were removed, weighed, and counted for total radioactivity in the gamma scintillation counter. The fraction of CO 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 calculated by multiplying the fraction of CO in each organ by the simultaneously measured cardiac output (reference method). The organ flow (per gram of tissue) and fractional distribution of cardiac output per gram of tissue were then calculated by dividing organ flow and fraction of cardiac output by the respective organ weight. Vascular resistance (index) for that organ was obtained by dividing mean arterial pressure by that organ flow (per gram of tissue). At the end of the experiment, femoral blood samples (0.5 ml) were collected and total plasma catecholamine levels were measured radioenzymatically by the method of Peuler and Johnson. After total brain radioactivity had been determined, the brain was placed in 10% formalin where it remained for at least 2 weeks. Localization of brain lesions was confirmed from frozen sections that were cut at 40 μ intervals and mounted on agar-coated glass slides and stained with toluidine blue and basic fuchsin.

Statistical evaluation of results was performed by standard techniques using unpaired $t$ test; $p < 0.05$ was considered to be significant.

Results

Immediate Responses

In agreement with previous studies, bilateral lesions of the anterior hypothalamus (AH) invariably resulted in a gradual increase in motor activity culminating in a most aggressive and irritable behavior. Thirty minutes after placement of the lesions and discontinuance of the ether anesthesia, mean arterial pressure (MAP) was significantly higher than that of the control (sham) group (fig. 1). Pressure continued to increase until the conclusion of the study. Associated with the pressure rise was a gradual increase in heart rate, which was significantly different 60 minutes after lesioning.

Hemodynamic Effects

Two hours after placement of the lesions, hemodynamic changes were measured (table 1). The AH lesions resulted in a significant elevation of both MAP (sham 111 ± 4 mm Hg; lesion 152 ± 3 mm Hg; $p < 0.001$) and total peripheral resistance (TPR) index (sham 0.419 ± 0.014 units; lesion 0.523 ± 0.018 units; $p < 0.001$) that was associated with increased circulating levels of norepinephrine ($p < 0.05$) and epinephrine ($p < 0.01$). Cardiac output tended to increase in lesioned animals, but the increase was not significant. The fractional distribution of cardiac output in the AH-lesioned rat was decreased to skin ($p < 0.001$), kidneys ($p < 0.001$), intestine ($p < 0.01$), liver ($p < 0.05$), pancreas ($p < 0.05$), spleen ($p < 0.005$), and testis ($p < 0.05$), and increased to skeletal muscle ($p < 0.05$) (table 2). This was also associated with an absolute reduction in blood flow to skin, kidneys, liver, intestine, spleen, and testis while skeletal muscle flow increased significantly.
result, organ vascular resistances increased in all organs except heart and skeletal muscle, but the greatest increases occurred in skin, kidneys, small intestine, spleen, stomach, and testis. Only skeletal muscle demonstrated a significant fall in vascular resistance.

Localization of Lesions

All of the lesions destroyed the bulk of the nucleus. Structures that bordered the lesion sites were the third ventricle, medially; the nucleus lateralis, laterally; chiasma opticum, and tractus opticus, ventrally; fornix, dorsally; preoptic nucleus, anteriorly; and nucleus dorsomedialis and nucleus ventromedialis, posteriorly. The adjacent periventricular structures between the nucleus and the third ventricle were destroyed. Rarely, minimal damage to the nucleus suprachiasmaticus and the rostral pole of the nucleus ventromedialis occurred.

To check the specificity of the changes in MAP produced by the AH lesion, we studied four rats with lesions in the lateral hypothalamus. Following the lesion, the blood pressure in these rats corresponded to the control group and no changes were noted in regional blood flows. No behavioral changes were noted.

Discussion

The present study confirms previous findings that indicated that bilateral AH lesions provoke markedly increased arterial pressure mainly as a result of increased TPR. That the increased TPR appears to be produced by a release of catecholamines from the adrenal medulla was shown by the prevention of AH hypertension by adrenalectomy in Nathan and Reis. In contrast, however, we did not observe a significant decrease in CO; our lesioned rats tended to have higher CO than control animals.

The acute increase in MAP that followed AH lesions in the present study was associated with significant changes in the distribution of CO. These changes were characterized by an increased blood flow to skeletal muscle and a decreased flow to skin, kidney, and splanchnic organs. These changes in the fractional distribution of cardiac output reflect in general similar
TABLE 2. Regional Hemodynamics in Sham Control (C) and Bilateral Anterior Hypothalamic Lesioned (L) Conscious Wistar Rats

<table>
<thead>
<tr>
<th>Organ</th>
<th>Fractional flow (% cardiac output/g)</th>
<th>Blood flow (ml/min/g)</th>
<th>Organ vascular resistance (mm Hg/ml/min/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>C 0.16 ± 0.02</td>
<td>0.14 ± 0.02</td>
<td>0.850 ± 0.068</td>
</tr>
<tr>
<td></td>
<td>L 0.08 ± 0.01;*</td>
<td>0.08 ± 0.02</td>
<td>1.863 ± 0.093;§</td>
</tr>
<tr>
<td>Muscle</td>
<td>C 0.13 ± 0.02</td>
<td>0.12 ± 0.02</td>
<td>1.082 ± 0.113;</td>
</tr>
<tr>
<td></td>
<td>L 0.19 ± 0.01;*</td>
<td>0.21 ± 0.01;*</td>
<td>0.753 ± 0.094;§</td>
</tr>
<tr>
<td>Brain</td>
<td>C 1.52 ± 0.39</td>
<td>1.31 ± 0.31</td>
<td>0.111 ± 0.012;</td>
</tr>
<tr>
<td></td>
<td>L 1.01 ± 0.04</td>
<td>1.05 ± 0.04</td>
<td>0.145 ± 0.004;*</td>
</tr>
<tr>
<td>Heart</td>
<td>C 5.16 ± 0.44</td>
<td>4.62 ± 0.51</td>
<td>0.026 ± 0.002;</td>
</tr>
<tr>
<td></td>
<td>L 6.47 ± 0.99</td>
<td>6.85 ± 1.10</td>
<td>0.026 ± 0.002;</td>
</tr>
<tr>
<td>Kidney</td>
<td>C 8.23 ± 0.49</td>
<td>7.34 ± 0.55</td>
<td>0.016 ± 0.002;</td>
</tr>
<tr>
<td></td>
<td>L 3.71 ± 0.36;§</td>
<td>3.90 ± 0.40;</td>
<td>0.043 ± 0.005;§</td>
</tr>
<tr>
<td>Small intestine</td>
<td>C 1.40 ± 0.12</td>
<td>1.30 ± 0.14</td>
<td>0.095 ± 0.010;</td>
</tr>
<tr>
<td></td>
<td>L 0.79 ± 0.09;†</td>
<td>0.83 ± 0.08;†</td>
<td>0.207 ± 0.026;§</td>
</tr>
<tr>
<td>Large intestine</td>
<td>C 0.92 ± 0.13</td>
<td>0.85 ± 0.16</td>
<td>0.166 ± 0.021;</td>
</tr>
<tr>
<td></td>
<td>L 0.45 ± 0.05;*</td>
<td>0.46 ± 0.05;*</td>
<td>0.362 ± 0.033;§</td>
</tr>
<tr>
<td>Liver</td>
<td>C 0.49 ± 0.09</td>
<td>0.42 ± 0.07</td>
<td>0.400 ± 0.091;</td>
</tr>
<tr>
<td></td>
<td>L 0.20 ± 0.03;†</td>
<td>0.21 ± 0.03;†</td>
<td>1.229 ± 0.512;</td>
</tr>
<tr>
<td>Pancreas</td>
<td>C 0.88 ± 0.07</td>
<td>0.80 ± 0.09</td>
<td>0.155 ± 0.015;</td>
</tr>
<tr>
<td></td>
<td>L 0.58 ± 0.07;†</td>
<td>0.62 ± 0.09</td>
<td>0.298 ± 0.042;</td>
</tr>
<tr>
<td>Spleen</td>
<td>C 2.26 ± 0.22</td>
<td>2.03 ± 0.23</td>
<td>0.061 ± 0.006;</td>
</tr>
<tr>
<td></td>
<td>L 0.79 ± 0.30;§</td>
<td>0.83 ± 0.31;†</td>
<td>0.345 ± 0.057;§</td>
</tr>
<tr>
<td>Stomach</td>
<td>C 0.97 ± 0.11</td>
<td>0.89 ± 0.13</td>
<td>0.145 ± 0.015;</td>
</tr>
<tr>
<td></td>
<td>L 0.55 ± 0.05;*</td>
<td>0.58 ± 0.06;*</td>
<td>0.290 ± 0.028;§</td>
</tr>
<tr>
<td>Splanchnic</td>
<td>C 0.94 ± 0.06</td>
<td>0.85 ± 0.07</td>
<td>0.137 ± 0.007;</td>
</tr>
<tr>
<td></td>
<td>L 0.47 ± 0.05;§</td>
<td>0.50 ± 0.05;§</td>
<td>0.327 ± 0.026;§</td>
</tr>
<tr>
<td>Testis</td>
<td>C 0.34 ± 0.03</td>
<td>0.30 ± 0.03</td>
<td>0.404 ± 0.041;</td>
</tr>
<tr>
<td></td>
<td>L 0.21 ± 0.02;*</td>
<td>0.21 ± 0.02;*</td>
<td>0.774 ± 0.069;§</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SE; n = 11. Variables were measured 2 hours after lesion placement. Probability factors are compared with sham control.

*p < 0.05.
†p < 0.01.
‡p < 0.005.
§p < 0.001.

changes in absolute organ blood flow. Consistent with these changes, there were also increased circulatory levels of both epinephrine and norepinephrine.

The increased blood flow to skeletal muscle is of particular importance because skeletal muscle constitutes approximately 50% of the body mass. Probably the most important determinant of increased muscle flow is exercise hyperemia, a local chemically mediated mechanism for supplying the necessary flow to active muscle. Secondarily, other vasoactive stimuli such as activation of sympathetic vasodilator nerves and circulating epinephrine may play a role.

The regional hemodynamic changes observed after the elevation in MAP in AH-lesioned rats are quite different from those observed in SHR and in Goldblatt hypertension. Cardiac output is distributed normally in SHR rats of this age with the exception of an increased flow fraction to the brain and heart. In Goldblatt hypertension, however, myocardial flow is increased and cutaneous and renal flow fractions are decreased. In unanesthetized rats with acute arterial hypertension produced by bilateral lesion of the nucleus tractus solitarii, there are significant changes in regional hemodynamics: a decrease in fractional blood flow to colon, skeletal muscle, and skin with an increase to heart. However, because of the decrease in CO the absolute blood flow remained unchanged to the heart, but decreased in most other tissues. Nucleus tractus solitarii lesions produced a generalized increase in sympathetic vasoconstrictor discharge resulting from central deafferentation of arterial baroreceptors. AH lesions, however, produced a different pattern with participation of adrenomedullary catecholamines and with obvious behavioral changes.

Hemodynamic changes in naturally-elicited fighting in cats during confrontation have been reported by Adams et al. and are similar to those observed during stimulation of the lateral hypothalamus in rats. The changes during fighting were not dissimilar from those during exercise. Anterior hypothalamic lesions produced cardiovascular changes similar to those seen during fighting and stimulation of the lateral hypothalamus.

The hemodynamic and behavioral changes produced by AH lesions could result not only from destruction of a specific nucleus, but also from destruction of fiber tracts passing through the anterior...
Hypothalamus which exert tonic inhibitory effects in other areas of the brain. These could be areas in the brain that are involved in the control of the adrenal medulla and also participate in the cardiovascular alterations observed during fighting and exercise.

These studies also show that the hemodynamic changes produced by two means of centrally-mediated adrenergic stimulation are highly different. On one hand, nucleus tractus solitarius lesions produce generalized organ vasoconstriction sparing, relatively, the coronary vasculature. The vasoconstriction produced by these lesions is unaffected by adrenalectomy. On the other hand, the systemic vasoconstriction that occurred after AH lesion is mediated by adrenomedullary catecholamines.

Acknowledgments

The authors thank Dr Allan A MacPhee for the catecholamine determinations.

References

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*Hypertension*. 1981;3:245-249
doi: 10.1161/01.HYP.3.2.245

*Hypertension* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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