Central Neural Mechanisms of the Cerebral Ischemic Response

Characterization, Effect of Brainstem and Cranial Nerve Transections, and Simulation by Electrical Stimulation of Restricted Regions of Medulla Oblongata in Rabbit

ROGER A.L. DAMPNEY, MAMORU KUMADA, AND DONALD J. REIS

SUMMARY The cerebral ischemic response was elicited in anesthetized rabbits by briefly clamping both common carotid arteries after previously occluding the vertebral arteries. The primary cerebral ischemic response, elicited after elimination of baroreceptors, consisted of arterial hypertension, bradycardia, and apnea. The hypertension resulted from a stereotyped and differentiated pattern of vasoconstriction in renal, mesenteric, and femoral arteries. Total peripheral conductance and cardiac output were decreased. Vagotomy usually changed the bradycardia to a tachycardia unaffected by adrenalectomy. With baroreceptors intact the magnitude of the bradycardia increased and its latency decreased. The ischemic response persisted after transection of brainstem at the pontomedullary junction and/or of lower cranial nerves (except for the bradycardia which was abolished by transection of vagal rootlets). Transection of the spinal cord at C1 abolished the reflex hypertension and apnea, but not the bradycardia. Hypertension and changes of regional blood flow, comparable qualitatively and quantitatively to those elicited by ischemia, were produced by electrical stimulation of areas of the medullary reticular formation encompassing portions of the gigantocellular and parvocellular reticular nuclei. We conclude: (1) the primary cerebral ischemic response is associated with a neurally mediated and differentiated pattern of vasoconstriction and with coactivation of the cardiac vagal and sympathetic nerves; (2) the reflex cardiac, but not vasomotor, components are secondarily modified by baroreceptor reflexes; (3) the ischemic response results from direct stimulation of neurons in the medulla oblongata; (4) the parvocellular and gigantocellular nuclei mediate the vasomotor but not the cardiac and respiratory components of the response. Circ Res 44: 48-62, 1979
determine whether the ischemic response was initiated by stimulation of receptors in the brain. Finally, we attempted to simulate the response by electrical stimulation of the medulla with micro-electrodes, thereby to identify and map regions of possible importance in its integration.

We shall demonstrate that the cerebral ischemic response is modified by baroreceptors, is characterized by a stereotyped and patterned change in peripheral blood flow due to direct stimulation of medullary neurons, and that the vasomotor but not the cardiovagal and respiratory components can be elicited by electrical stimulation of highly localized regions of dorsal portions of the medullary reticular formation. In the following paper (Kumada et al., 1979) we shall demonstrate that lesions only of this region will abolish the vasomotor component of the reflex. A preliminary report on parts of the study has been made (Dampney et al., 1975).

Methods

Principle of Method

The cerebral ischemic response was elicited in the rabbit by a modification of the method of Miyakawa (1966). With this method, both vertebral arteries are occluded within their passage through the cervical vertebrae. The cerebral circulation, which is then entirely provided by the common carotid arteries, is then interrupted by compressing the carotid arteries, eliciting thereby a cerebral ischemic response. The rabbit is a particularly useful species for this analysis since, in contrast to the dog (Hill, 1900), total ischemia of the brain can be produced by arresting blood flow through both pairs of common carotid and vertebral arteries.

Surgical Procedures

General

Experiments were performed on 86 New Zealand white rabbits of both sexes (3.0–5.0 kg) anesthetized with urethane (1.25 g/kg, iv) after induction of anesthesia, the trachea was cannulated and polyethylene catheters were placed in a femoral artery and vein. The aortic depressor nerves were sectioned in the neck except in those experiments designed to examine the participation of aortic baroreceptors in the response. The rectal temperature was monitored and maintained in the range of 37–38°C by a thermostatically regulated heating pad.

Except for rabbits in which cerebral ischemia was not produced, the vertebral arteries were then occluded. The portions of the trachea and esophagus overlying the 2nd, 3rd, and 4th cervical vertebrae were ligated and excised, exposing the longus colli and longus capitis muscles. These muscles then were cut over the 3rd vertebra exposing the longus colli and vein. The aortic depressor nerves were sectioned with urethane (1.25 g/kg, iv) after induction of anesthesia. After this general preparation, one or more of the following procedures were performed either immediately or after control observations.

Placement of Flow Probes

For experiments in which blood flows were measured, a flow probe (Carolina Medical Electronics model EP-403R, EP-404R, or EP406R, or Narco Bio-Systems C series 1.0 or 1.5 mm i.d.) was applied to one of the following arteries: (1) the right or left femoral artery; (2) the right or left renal artery, approached retroperitoneally, with care taken to avoid damage to the renal nerves; (3) the superior mesenteric artery, approached through the midline ventral incision, with care taken to avoid damage to the sympathetic nerves; (4) the ascending aorta, approached through a thoraco-
omy in which the sternum was split transversely at the level of the third intercostal space, the ribs widely retracted, the pericardium incised, and the root of the aorta exposed. After placement of each flow probe, the appropriate incision was closed as completely as possible.

**Denervation of Arterial Baroreceptors**

The carotid bifurcations were denervated in some experiments under a dissecting microscope by stripping the adventitia from the walls of the carotid sinus and common, external, and internal carotid arteries to a distance of 5 mm from the sinus on each side. The tissue between the internal and external carotid arteries was ligated and cut. The aortic baroreceptors were denervated by sectioning the aortic nerves in the neck. The efficacy of denervation was demonstrated by the absence of a reflex bradycardia in response to administration of a bolus of norepinephrine in a dose sufficient to elevate the arterial pressure by 60–80 mm Hg.

**Bilateral Adrenalectomy**

This was performed by ligating the hilus of each adrenal gland near the abdominal vena cava, as described by White (1966).

**Peripheral Denervation Procedures**

The femoral vascular bed was denervated by sectioning the femoral and sciatic nerves. The renal, adrenal gland near the abdominal vena cava, as described by White (1966). The carotid bifurcations were denervated in some experiments under a dissecting microscope by stripping the adventitia from the walls of the carotid sinus and common, external, and internal carotid arteries to a distance of 5 mm from the sinus on each side. The tissue between the internal and external carotid arteries was ligated and cut. The aortic baroreceptors were denervated by sectioning the aortic nerves in the neck. The efficacy of denervation was demonstrated by the absence of a reflex bradycardia in response to administration of a bolus of norepinephrine in a dose sufficient to elevate the arterial pressure by 60–80 mm Hg.

**Regional blood flows** were recorded by either of two square-wave electromagnetic flow meters (Carolina Medical Electronics model 501, or Narco Biosystems model RT-400), connected to a flow probe implanted on the ascending aorta or on the femoral, renal, or superior mesenteric artery as described above. In most experiments, blood flow was measured through only one artery. The zero level of flow was established in situ before and after an experimental series by occluding the artery distal to the probe. The probes were calibrated by passing, at different flow rates, saline or whole blood through an isolated arterial segment to which the probe was attached.

**Respiration** was assessed by measuring intrathoracic pressure through a polyvinyl chloride balloon catheter implanted in the thorax between the lungs and the pleura.

**Drug Interventions**

Propranolol (Inderal, Ayerst Inc.; 1 mg/kg, im) was administered to block β-adrenergic cardiac receptors. Alpha-receptors were blocked with either phenoxybenzamine (Dibenzyline, Smith, Kline & French Ltd.; 20 mg/kg, iv) or phentolamine (Regitine, Ciba Pharmaceutical Co.; 1 mg/kg, im). The efficacy of α-receptor blockade was demonstrated by the lack of effect of a challenging dose of norepinephrine solution (levarterenol, Levophed, Winthrop Laboratories; 4 μg/ml). In those experiments in which the arterial pressure fell precipitously after transection of the spinal cord at C1, norepinephrine (4 μg/ml) was infused by intravenous drip to restore and maintain normal arterial pressure.

**Electrical Stimulation**

The brainstem was explored stereotaxically with monopolar stimulating electrodes. The electrodes were made of Teflon-coated stainless steel wire (150 μm o.d.) bare at the tip for 50 μm. The electrode wire was carried in no. 28 stainless steel hypodermic tubing, but protruded through the end of the tubing by about 10 mm. Only the electrode wire entered the brain tissue.

The electrodes were inserted perpendicularly into the brainstem under direct vision using a dissecting microscope. In some experiments, the vermis of the caudal cerebellum was first removed by gentle aspiration to expose the more rostral part of the dorsal surface of the brainstem. The lateral and rostro-caudal coordinates of each electrode track were referred to the obex, and the dorsal-ventral

**Arterial blood pressure** was recorded from the femoral arterial catheter connected to a strain-gauge transducer (Statham P23Db). The mean arterial pressure and heart rate were computed from the arterial pressure signal by a low-pass filter (Beckman, A-C coupler type 9806A) and cardiotochometer (Beckman, type 9857), respectively. The arterial pressure, mean arterial pressure, heart rate, and all other data signals were displayed on channels of a polygraph (Beckman, Dynograph recorder type 506A).

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coordinates to the dorsal surface of the brainstem. Tracks were explored in steps of 0.5 mm. For subsequent identification of stimulation sites, each tract was marked at two spots by passing a current of 20 μA for 30 seconds in order to deposit iron at the electrode tip.

The stimuli, which were applied at each step, consisted of negative square-wave pulses of 0.5-msec duration, delivered from a Tektronix pulse generator through an RF stimulus isolation unit. The stimulus current, measured by passing the stimulus across a 10 Ω resistor, was amplified by a Tektronix 122 preamplifier and was displayed on an oscilloscope (Tektronix 360) and monitored throughout the experiment. The stimuli usually consisted of a 12-sec train of pulses of 100 μA amplitude and 50 Hz. Occasionally the duration of the pulse train was extended up to 50 seconds.

Histological Confirmation

At the end of the experiment each rabbit was killed by perfusion through the heart with saline followed by 10% formaldehyde and 1% each of potassium ferro- and ferricyanide to identify the position of marked spots by the Prussian blue reaction. The brains were then fixed and later were frozen and sectioned at every 50 μm. The sites of iron deposition were identified after the sections were stained for cells with cresyl violet. The localization of brain nuclei was made with reference to the atlas of Meesen and Olszewski (1949). In the experiments in which large lesions were made, the brain was perfused with saline followed by 10% formaldehyde solution. Later, after fixing, these brains were examined under a dissecting microscope to determine the extent of the lesions.

Data Analysis

Total peripheral conductance was calculated by dividing the mean ascending aortic flow by the mean arterial pressure. Regional vascular conductance (RVC) in a given vascular bed was calculated from the formula \( RVC = \frac{Fm}{Pm} \), where \( Fm \) and \( Pm \) represent the mean blood flow to that bed and mean arterial pressure, respectively. Conductance was preferred as a measure of vascular changes rather than its reciprocal, resistance. The reason for this is that, in some experiments during cerebral ischemia, renal blood flow decreased to nearly zero. Dividing the mean arterial pressure by a very small value yielded extremely large values of resistance, with the result that the calculation of the mean value of renal vascular resistance was biased by one or two very large numbers, a limitation avoided by calculating conductance.

The RVC during a period of cerebral ischemia was calculated both in absolute units (ml/min per mm Hg) and in relative units (percentage of control). The test value of RVC in a particular trial was the value at the point where the change in RVC was maximal during a 50-second period of cerebral ischemia. Usually, these measurements were made for two or three trials in each experiment to establish the reproducibility of the response in that rabbit. If the particular vascular bed under study was then denervated, two or three further trials were performed. The mean absolute and relative values of RVC during cerebral ischemia for the intact and denervated vascular bed were then calculated for each experiment and grouped with corresponding values from other experiments to determine the overall mean and standard error for each of the femoral, renal, and mesenteric beds in both the intact and denervated states. The same procedure was used for all other cardiovascular parameters, and also for determining changes in these variables elicited by electrical stimulation. Comparisons between means were made using Student’s t-test (Snedecor, 1967).

Results

The Primary Cerebral Ischemic Response

The Integrated Response Prior to Denervation of Baroreceptors

Cerebral ischemia in rabbits with intact baroreceptors elicited a large increase in mean arterial pressure and a fall in heart rate (Fig. 1, Table 1); in spontaneously breathing rabbits there was expiratory apnea (Fig. 1a). The onset latency of changes in arterial pressure was short (3–4 seconds) while for the respiratory response it was much longer (10–15 seconds). Detailed observations of cardiovascular changes were made in paralyzed and artificially ventilated animals to eliminate the secondary effects of systemic hypoxia on circulatory function (Korner, 1965) produced by apnea.

The rise of arterial pressure was due entirely to marked elevation in peripheral resistance (measured as a fall of total peripheral conductance) to a mean of 23% of control (Fig. 1b, Table 1). The peripheral vasoconstriction was primarily due to excitation of α-adrenergic receptors since α-receptor blockade in four rabbits reduced the pressor response from 89.5 ± 7.3 (mean ± SEM) to 13.3 ± 2.3 mm Hg.

Cardiac output during ischemia, measured by changes in ascending aortic blood flow, fell to a mean of 42% of control (Fig. 1b, Table 1). The fall of cardiac output was attributable to the increase in peripheral resistance and not the change in heart rate, since vagotomy, while abolishing the bradycardia (see below), did not alter the reduction in aortic flow or peripheral conductance (Fig. 1b).

Effects of Baroreceptor Denervation on the Ischemic Response

To assess the contribution of baroreceptors, the cerebral ischemic response was studied following interruption of baroreceptor afferents. Sinoaortic denervation or aortic denervation alone did not alter the magnitude of changes in arterial pressure;
(a) The cerebral ischemic response in a spontaneously breathing anesthetized rabbit. Abbreviations: Exp, expiration; Insp, inspiration; ITP, intrathoracic pressure. In this and subsequent figures, the bar at the base represents the period of ischemia. (b) Effects of aortic nerve transection alone and in conjunction with vagotomy on the cerebral ischemic response. Denervation of aortic baroreceptors does not affect the changes in arterial pressure, ascending aortic flow, or total peripheral conductance but greatly reduces and delays the bradycardia. Note also that, in this experiment, following denervation the bradycardia during ischemia was preceded by a slight tachycardia. Immediately after cessation of ischemia (removal of carotid clips) there was a second transient bradycardia; this was probably a reflex arising from the carotid sinus baroreceptors being suddenly subjected to the elevated systemic arterial pressure. After vagotomy, ischemia elicited tachycardia.

### Table 1: Effect of Baroreceptor Denervation on Changes in Cardiovascular Variables during Cerebral Ischemia

<table>
<thead>
<tr>
<th></th>
<th>MAP (mm Hg)</th>
<th>HR (beats/min)</th>
<th>AAF (ml/min)</th>
<th>TPC (ml/min per mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>After aortic denervation</td>
<td>P value*</td>
<td>After sino-aortic denervation</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>10</td>
<td>104.7 ± 2.3</td>
<td>102.0 ± 2.3</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Test</td>
<td>183.4 ± 3.1</td>
<td>180.3 ± 2.5</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Difference</td>
<td>78.7 ± 2.5</td>
<td>78.3 ± 2.3</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>P value‡</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>10</td>
<td>318 ± 18</td>
<td>315 ± 4</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Test</td>
<td>171 ± 18</td>
<td>280 ± 7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Difference</td>
<td>-147 ± 15</td>
<td>-35 ± 6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>P value‡</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AAF (ml/min)</td>
<td>4</td>
<td>293 ± 29</td>
<td>296 ± 29</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Test</td>
<td>126 ± 21</td>
<td>122 ± 15</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Difference</td>
<td>-167 ± 15</td>
<td>-174 ± 16</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>P value‡</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>NS</td>
</tr>
<tr>
<td>TPC (ml/min per mm Hg)</td>
<td>4</td>
<td>2.89 ± 0.39</td>
<td>2.77 ± 0.28</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Test</td>
<td>0.68 ± 0.11</td>
<td>0.65 ± 0.08</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Difference</td>
<td>-2.21 ± 0.30</td>
<td>-2.12 ± 0.23</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>P value‡</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SEM. Abbreviations: MAP = mean arterial pressure; HR = heart rate; AAF = ascending aortic flow; TPC = total peripheral conductance.

*Represents statistical significance of difference (intact vs. aortic denervated). NS = not significant (P > 0.05).

†Represents statistical significance of difference (intact vs. sino-aortic denervated). In all cases differences between values in aortic and sino-aortic denervated groups are not significant.

‡Represents statistical significance of difference (control vs. test).
moreover, the changes in pressure produced by either procedure did not differ from each other (Table 1). Aortic denervation did not change the magnitude of the reduction in either aortic flow or total peripheral conductance elicited by ischemia (Fig. 1b, Table 1).

In contrast, interruption of baroreceptor afferents usually markedly reduced and, less commonly, even abolished or reversed the reflex bradycardia. Thus, in 28 of 36 rabbits in which only the aortic nerves were sectioned, and in five of six subjected to sinoaortic denervation, the bradycardia was significantly reduced (Fig. 1b, Table 1). Baroreceptor denervation also increased the onset latency for the bradycardia from 10.6 ± 1.1 (mean ± SEM) to 21.3 ± 1.4 seconds (P < 0.001). Occasionally, after ablation of baroreceptors, the residual bradycardia was preceded by a slight tachycardia (e.g., Fig. 1b). In the remaining nine rabbits, the bradycardia was abolished or reversed to a slight tachycardia. In the remaining nine rabbits, the bradycardia was abolished or reversed to a slight tachycardia. These observations indicate that during cerebral ischemia baroreceptor reflex mechanisms substantially contribute to the reflex bradycardia but not the hypertension.

Efferent Cardiovascular Mechanisms of the Primary Response to Cerebral Ischemia

Since there were no significant differences in the cardiovascular responses to cerebral ischemia in rabbits with total sinoaortic denervation or aortic denervation alone, the primary cardiovascular response to cerebral ischemia was further analyzed in rabbits in which only the aortic nerves were transected.

Vasomotor Responses. Changes in blood flow and vascular conductance in the femoral, mesenteric, and renal arteries elicited by cerebral ischemia were measured in 19 rabbits. The relative changes are indicated in Figure 2, absolute values in Table 2.

Vasoconstriction occurred in all three beds (Fig. 2, Table 2). However, the degree of vasoconstriction in the renal bed was significantly greater (P < 0.001) than in the femoral or mesenteric beds (which did not differ from each other). The vasoconstriction in each bed was significantly reduced by sympathetic denervation (Fig. 2, Table 2). After sympathectomy some residual vasoconstriction persisted in the renal and mesenteric beds; in the femoral bed, however, the response was reversed to vasodilation. The residual mesenteric vasoconstriction and femoral vasodilation were abolished by bilateral adrenalec- tomy.

Thus, cerebral ischemia results in a differentiated pattern of peripheral vasoconstriction primarily mediated by sympathetic nerves. Although adrenergic catecholamines also are released, they do not contribute to the peak responses, and probably produce only poststimulus effects such as vasodilation in the femoral and vasoconstriction in the renal and mesenteric beds.

Heart Rate Response. Vagotomy invariably abolished the reflex bradycardia elicited by cerebral ischemia. Moreover, after vagotomy there was, in most instances, a small but significant increase in heart rate (Fig. 1b, Table 3A). The tachycardia that persisted after vagotomy was virtually abolished after β-adrenergic blockade with propranolol (Table 3A) but not by bilateral adrenalectomy (Table 3B). These findings indicate that during ischemia both cardiovagal and cardiac sympathetic nerves are coactivated.

Effects of Transection of the Brainstem, Cranial Nerves or Cervical Cord on the Cerebral Ischemic Response

To establish if the cerebral ischemic response was initiated by stimulation of receptors extracerebrally or within brain itself, we analyzed, in 14 rabbits, the effects on the cardiovascular responses to ischemia of transection of the brainstem and/or cranial nerves (see Fig. 3 and Table 4).

Transection of the brainstem at the level of the
TABLE 2 Changes in Regional Blood Flows and Vascular Conductances during the Cerebral Ischemic Response before and after Sympathetic Denervation

<table>
<thead>
<tr>
<th>Region</th>
<th>Control</th>
<th>Test</th>
<th>Difference</th>
<th>P value (control vs. test)</th>
<th>Control</th>
<th>Test</th>
<th>Difference</th>
<th>P value (control vs. test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femoral bed</td>
<td>Intact</td>
<td>11.1±0.8</td>
<td>8.7±1.3</td>
<td>-2.4±1.2</td>
<td>NS</td>
<td>0.102±0.006</td>
<td>0.061±0.008</td>
<td>-0.05±0.006</td>
</tr>
<tr>
<td></td>
<td>Denervated</td>
<td>11.7±1.1</td>
<td>23.1±2.2</td>
<td>11.4±1.9</td>
<td>&lt;0.001</td>
<td>0.111±0.101</td>
<td>0.153±0.014</td>
<td>0.042±0.012</td>
</tr>
<tr>
<td>Mesenteric bed</td>
<td>Intact</td>
<td>80.3±16.5</td>
<td>54.6±10.4</td>
<td>-25.7±15</td>
<td>&lt;0.01</td>
<td>0.897±0.115</td>
<td>0.304±0.050</td>
<td>-0.393±0.066</td>
</tr>
<tr>
<td></td>
<td>Denervated</td>
<td>101.6±29.8</td>
<td>21.2±14.6</td>
<td>-80.4±15.2</td>
<td>NS</td>
<td>0.985±0.202</td>
<td>0.685±0.186</td>
<td>-0.302±0.056</td>
</tr>
<tr>
<td>Renal bed</td>
<td>Intact</td>
<td>31.6±8.3</td>
<td>3.2±0.9</td>
<td>-28.4±8.5</td>
<td>&lt;0.01</td>
<td>0.328±0.092</td>
<td>0.018±0.005</td>
<td>-0.310±0.093</td>
</tr>
<tr>
<td></td>
<td>Denervated</td>
<td>38.8±13.2</td>
<td>-0.5±4.7</td>
<td>NS</td>
<td>0.468±0.124</td>
<td>0.232±0.073</td>
<td>-0.236±0.055</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SEM. NS = not significant (P > 0.06).

TABLE 3 Contribution of Cardiac Vagal, Cardiac Sympathetic, and Adrenomedullary Activation to the Primary Cardiac Response to Cerebral Ischemia

<table>
<thead>
<tr>
<th>Heart rate (beats/min)</th>
<th>P value (control vs. test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n Control Test Difference</td>
<td></td>
</tr>
</tbody>
</table>

A. Effect of vagotomy and subsequent β-receptor blockade by propranolol

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Control</th>
<th>Test</th>
<th>Difference</th>
<th>P value (control vs. test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac efferents intact</td>
<td>40</td>
<td>308±5</td>
<td>272±7</td>
<td>-36±6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>After subsequent vagotomy</td>
<td>18</td>
<td>296±9</td>
<td>32±10</td>
<td>32±6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P value (intact vs. vagotomized)</td>
<td>NS</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>After subsequent β-blockade</td>
<td>7</td>
<td>214±8</td>
<td>221±8</td>
<td>7±2</td>
<td>NS</td>
</tr>
<tr>
<td>P value (vagotomized vs. after β-blockade)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.05</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

B. Effect of adrenalectomy after vagotomy

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Control</th>
<th>Test</th>
<th>Difference</th>
<th>P value (control vs. test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vagotomized</td>
<td>4</td>
<td>341±12</td>
<td>42±6</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>After subsequent adrenalectomy</td>
<td>4</td>
<td>331±11</td>
<td>24±4</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>P value (vagotomized vs. adrenalectomized)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SEM. NS = not significant (P > 0.06).
FIGURE 3  Effect of transection of the brainstem at the pontomedullary junction, subsequent section of the roots of cranial nerves VII-XI, and of transection of the spinal cord at C1 on the cerebral ischemic response. Panels a-c represent results from one rabbit: (a) control response; (b) response following brainstem transection at the pontomedullary junction; (c) response following subsequent section of cranial nerves VII-XI. Note that the response persisted after both pontomedullary transection and subsequent section of all cranial nerve inputs to the medulla, although baseline arterial pressure fell after section of the cranial nerves due to bleeding. Panels d and e represent another animal: (d) control response; (e) response following spinal cord transection. After spinal cord transection, arterial pressure was maintained by norepinephrine infusion. Note that after C1 transection the pressor response has virtually disappeared whereas the heart rate response has altered from practically no change to a bradycardia. In this and all subsequent figures, unless specified, the rabbits were anesthetized, paralyzed, and artificially ventilated.

TABLE 4  Effect of Gross Brain Lesions on the Cerebral Ischemic Response

<table>
<thead>
<tr>
<th></th>
<th>Mean arterial pressure (mm Hg)</th>
<th>Heart rate (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n Control Test Difference P value (control vs. test) Control Test Difference P value (control vs. test)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact</td>
<td>100±2±2.5 179.2±2.4 79.0±5.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>After C1 transection</td>
<td>6† 107.6±0.9 8.8±1.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P value (intact vs. transected)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>After subsequent vagotommy</td>
<td>3 97.0±3 107.3±2.4 10.3±2.7</td>
<td>NS</td>
</tr>
<tr>
<td>P value (transected vs. vagotomized)</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± se. NS = not significant (P >0.05).
† In three of these experiments the heart rate was not measured.
‡ In one of these experiments the heart rate was not measured.
tion of restricted areas of the medulla (Fig. 4). With a 12-second stimulus train of fixed intensity (100 μA), the responses appeared at a stimulus frequency of 5–10 Hz and were optimal between 50 and 200 Hz. Although a stimulus train of rectangular pulses (50 Hz, 0.5-msec pulse width, 12-second train) of a suitable stimulus current elicited the pressor response over many millimeters along an electrode track (Figs. 4 and 5), the zone from which an elevation of mean arterial pressure greater than 50 mm Hg could be elicited, with a current of 100 μA, was limited vertically to less than 1.5 mm (Fig. 5). Measurement of the threshold current (i.e., the minimal current required for eliciting a rise of mean arterial pressure greater than 10 mm Hg) along the same track demonstrated a close inverse relationship to the magnitude of the pressor response and threshold current (Fig. 5). For purposes of surveying the medulla, we therefore defined a positive point as a site along an electrode track which, when stimulated with a 12-second train of 50 Hz at 100 μA, elicited an increase of arterial pressure of 50 mm Hg or greater.

Distribution of Positive Points

One hundred tracks were explored and 814 points stimulated in nine rabbits. The results are summarized in Figure 6. Positive points (filled circles) were largely confined to the dorsal portions of the medullary reticular formation. The caudal extent of the positive region was at the level of the middle of the inferior olivary nucleus (Fig. 6d); the rostral extent was at the level of entry of the facial nerve (Fig. 6a). In its cross-sectional shape and area, the positive area was approximately circular, reaching its greatest diameter at the level of the medial portion of the facial nucleus (5.0–6.0 mm rostral to the obex, Fig. 6b). Rostral or caudal to this zone, few positive sites were found (e.g., Fig. 6d).

Throughout its rostro-caudal extent the responsive region paralleled the trigeminal nucleus but was approximately 1.5 mm medial to it. The positive region did not conform in its entirety to any single nucleus of the reticular formation. Rather it primarily overlapped two reticular nuclei identified by Meesen and Olszewski (1949) as the nucleus reticularis parvocellularis and the dorsal portions of the nucleus gigantocellularis, particularly at a level corresponding to the medial portion of the facial nucleus (Fig. 6b), the site from which the largest responses were obtained. The positive area also lies within the trajectory of the central tegmental tract and ascending noradrenergic bundles.

*Physiological Characteristics of the Evoked Response*

*Changes in Heart Rate and Respiration.* During electrical stimulation of the medullary pressor area in rabbits with intact baroreceptors, the heart rate
**Figure 5** Relationship between the magnitude of the elevation of arterial pressure elicited by electrical stimulation with a fixed intensity (100 μA) and a threshold current required to elicit a rise of arterial pressure of 10 mm Hg at points 0.5 mm apart in an electrode track passing through the reticular formation of the rabbit medulla. Left panel indicates sites (small filled circles). Large filled circles indicate positive points (i.e., arterial pressure rise greater than 50 mm Hg produced by standard stimulus). Right panel indicates depth of electrode on ordinate and either threshold current (open circles, μA) or arterial pressure rise (closed circles, mm Hg) on the abscissa. Note the reciprocal relationship between the two variables and the correspondence between the sites of lowest threshold and maximal response. Abbreviations as in Figure 4.

**Figure 6** Distribution of positive sites in the brainstem of nine rabbits. All points were grouped on four representative sections taken at different levels anterior (rostral) to the obex. Large filled circles mark points where the pressor response was associated with bradycardia, whereas the crossed circles mark points where the pressor response was accompanied by little change in heart rate, or a slight bradycardia. Small filled circles are negative sites. See text for details. Abbreviations as in Figure 4.
response was variable, although most commonly a small bradycardia was evoked (Table 6). After sino-aortic denervation, stimulation of points throughout the pressor area in all cases (Table 6) failed to elicit bradycardia (Fig. 7a). This baroreceptor-dependent bradycardia stands in contrast to that associated with cerebral ischemia, which, as demonstrated above, is in part independent of baroreceptor reflexes.

Electrical stimulation of the pressor area in two spontaneously breathing rabbits (one of which was baroreceptor-denervated) increased respiratory rate and depth (Fig. 7b), in contrast to the apnea always observed in response to cerebral ischemia (Fig. 1a).

Changes in Regional Blood Flow and Vascular Resistance

We sought to determine whether the pattern and magnitude of the regional vascular changes elicited by electrical stimulation within the pressor area were comparable to those elicited by cerebral ischemia. Thus, in seven rabbits, in addition to arterial pressure and heart rate, blood flow in the femoral and/or renal arteries was measured during stimulation at positive sites. In all of these experiments, the aortic nerves were sectioned and the vertebral arteries occluded to allow a comparison in the same rabbits of the responses to electrical and ischemic stimulation (Fig. 8).

Stimulation of positive points always elicited a decrease in femoral and renal conductance, with vasoconstriction always more marked in the renal bed. The threshold for the response varied between 15 and 20 μA, and the response was graded with respect to stimulus current. The absolute changes in arterial pressure, heart rate, femoral and renal flows, and conductances elicited by a stimulus of 5 times threshold are summarized in Table 6. A comparison with Table 2 demonstrates that the renal and femoral vasomotor responses to electrical and ischemic stimuli are very similar in magnitude.

An analysis was made of the relationship between stimulus intensity and the evoked change in arterial pressure and femoral and renal conductances. The results, illustrated in Figure 8, emphasize several features of the responses: (1) The changes in arterial pressure and conductances in the femoral and renal beds have a comparable threshold and are graded with respect to stimulus intensity. (2) Whereas a maximal elevation in arterial pressure is obtained with a stimulus intensity approximately 10 times threshold, maximal vasoconstriction of the renal bed occurs at 4 times threshold. In contrast, in the femoral bed, a clear plateau is not reached even at 20 times threshold. (3) The reduction in conductance (vasoconstriction) in the renal bed is significantly greater than in the femoral bed at all levels of stimulus current ($P < 0.01$ or $< 0.05$).

Over the stimulus intensity range of 4–10 times threshold, the relative magnitude of changes in arterial pressure and in femoral and renal arterial conductances did not differ significantly from those elicited in other animals by cerebral ischemia (Fig. 8b). In four experiments on the same rabbits, the medulla was stimulated and cerebral ischemia was produced. In these rabbits electrical stimulation at 4–10 times threshold and cerebral ischemia elicited qualitatively and quantitatively comparable changes in arterial pressure and femoral and renal vascular conductances.

The results demonstrate that electrical stimulation of the positive areas of the medulla elicits vasomotor changes that are identical qualitatively and quantitatively to those elicited by ischemia.

Table 5  Effect of Sinoaortic Denervation on Changes in Mean Arterial Pressure and Heart Rate in Response to Electrical Stimulation of the Medullary Pressor Area

<table>
<thead>
<tr>
<th>Baroreceptors intact</th>
<th>n</th>
<th>Control</th>
<th>Test</th>
<th>Difference</th>
<th>$P$ value (control vs. test)</th>
<th>Control</th>
<th>Test</th>
<th>Difference</th>
<th>$P$ value (control vs. test)</th>
</tr>
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<tbody>
<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>After sino-aortic denervation</td>
<td>6†</td>
<td>102.3±6.5</td>
<td>170.1±5.7</td>
<td>67.8±7.5</td>
<td>0.001</td>
<td>301±5</td>
<td>312±5</td>
<td>11±3</td>
<td>&lt;0.06</td>
</tr>
</tbody>
</table>
| * Bradycardia was the predominant response in seven of these nine rabbits.† Bradycardia was not elicited in any of these rabbits.

Data are expressed as mean ± SEM. NS = not significant ($P > 0.05$).

Discussion

The Primary Cerebral Ischemic Response

This study has confirmed and elaborated upon the long-standing observations that the primary response to cerebral ischemia consists of arterial hypertension (McDowell, 1933; Guyton, 1948; Sagawa et al., 1961; Downing et al., 1963; Miyakawa, 1966), bradycardia (McDowell, 1933; Levy et al., 1968; Borison and Domjan, 1970), and apnea (Guyton, 1948; Levy et al., 1968) and that the rise in arterial pressure is due to increased peripheral resistance caused by intense vasoconstriction (Downing et al., 1963; Shimizu and Miyakawa, 1968). The
vasoconstriction is primarily neurogenic and is mediated by $\alpha$-adrenergic receptors. Simultaneously, cardiac output (as indicated by ascending aortic flow) falls by more than 50%. Since this marked fall in cardiac output persists after vagotomy combined with $\beta$-receptor blockade, it probably is not neurogenic but possibly is due to ventricular overload secondary to vasoconstriction (Guyton, 1955).

By assessing changes in flow and conductance in different vascular beds we have demonstrated, for the first time, that during cerebral ischemia the pattern of regional vasoconstriction, previously clearly defined only for the renal circulation (Murata and Miyakawa, 1967), is highly stereotyped, differentiated, and primarily neurogenic. Vasoconstriction is much more intense in the renal than in the femoral and mesenteric beds. Since denervation of the femoral, renal, and mesenteric beds did not unmask significant differences in resting sympathetic tone, it seems likely that the greater effect on the renal bed reflects a greater central activation of sympathetic outflow to the kidney in comparison to the other beds. Alternatively, it is possible that in the control state the skeletal muscle and mesenteric beds are relatively vasoconstricted, whereas the renal bed is relatively vasodilated with respect to their potential ranges. In that case, the difference in response may be due, at least in part, to differences in the vascular resistance change in each bed and to the same change in sympathetic vasomotor activity.

The primary cardiac response to cerebral ischemia usually is vagal bradycardia. The fact that, after vagotomy, ischemia elicits a tachycardia that can be abolished by $\beta$-adrenergic blockade but not by adrenalectomy, indicates that cerebral ischemia results in co-activation of both cardiac sympathetic and cardiac vagal nerves, the vagal inhibitory effect usually being predominant. This observation is in agreement with the findings of most (Anrep and Segall, 1926; McDowell, 1933; Levy et al., 1968), but not all (Guyton, 1948), investigators.

In this study we have examined, for the first time, the role of baroreceptor reflexes in the integrated response to cerebral ischemia. Our results demonstrated that denervation of the aortic baroreceptors, alone or in combination with those of the carotid sinus, did not influence the magnitude of changes in arterial pressure, cardiac output, or total peripheral conductance. In contrast, abolition of baroreceptor reflexes substantially reduces the magnitude and increases the latency for the reflex bradycardia. Thus, baroreceptor reflexes augment the excitation of medullary cardiovagal neurons directly stimulated by brainstem ischemia.

Such reinforcement of a centrally mediated cardiovagal response by peripheral receptors is comparable to the interaction between central and peripheral chemoreceptor reflexes acting upon the heart rate during the diving response (Jones and Purves, 1970). This interaction between the primary cardiovascular response to cerebral ischemia and baroreceptor reflexes contrasts with that occurring in another centrally organized cardiovascular response, the defense reaction (Djojosugito et al., 1970; Gebber and Snyder, 1970; Humphreys et al., 1971) in which the cardiac component of the baroreceptor reflex is suppressed. These observations reinforce the view that the cardiac and vasomotor components of the baroreceptor reflex can be dissociated, and each separately controlled by other regions of the brain (Djojosugito et al., 1970; Gebber and Snyder, 1970; Humphreys et al., 1971).

Role of the Medulla Oblongata in Mediating the Response

The cerebral ischemic reflex was unaffected by transection of the brainstem at the level of entry of the facial nerve (pontomedullary transection). Sub-
The ischemic response cannot be due to stimulation of receptors lying outside of the brain since interruption of projections of cranial nerves to bulbospinal vasomotor pathways, either by pontomedullary transection (nerves I-VII/VIII) or transection of lower cranial nerves (IX-XI), failed to block the reflex response; (2) that the ischemic response is fully integrated within the medulla oblongata and is elicited by direct stimulation of receptors in the medulla; and (3) that the bradycardia elicited by cerebral ischemia is due, in part, to excitation of cardiovagal neurons within the brainstem. Thus we have demonstrated for the first time that the cerebral ischemic response, like the comparable cardiovascular response elicited by increased intracranial pressure (the Cushing response (Hoff and Reis, 1970)), is evoked by direct stimulation of receptors within the brain.

Within the medulla a search was made for localized regions which, when focally stimulated, elicited cardiovascular changes that simulated the cerebral ischemic response. In many studies by other workers the medulla has been stimulated in a similar fashion and arterial pressure changes measured (Wang and Ranson, 1939; Alexander, 1946; Amoroso et al., 1954; Chai and Wang, 1962; Kahn and Mills, 1967; Gootman and Cohen, 1971; Coote et al., 1973; Troth et al., 1973). However, our approach differs from previous work in two major respects. First, whereas in some studies a single parameter of regional vasomotor activity was measured, such as, for example, splanchnic nerve activity (Kahn and Mills, 1967; Gootman and Cohen, 1971), cardiac sympathetic activity (Alexander, 1946), or skeletal muscle blood flow (Coote et al., 1973), in none of these studies were regional vasomotor changes measured within more than one vascular bed in response to stimulation of the medulla. Second, in nearly all previous studies either heart rate was not recorded (Wang and Ranson, 1939; Alexander, 1946; Amoroso et al., 1954) or, if recorded, the vagi were cut (Chai and Wang, 1962; Kahn and Mills, 1967; Gootman and Cohen, 1971). Since the regional vasomotor and heart rate changes evoked by cerebral ischemia were so characteristic and stereotyped, and differed so clearly from those associated with other pressor responses, such as the defense reaction (Coote et al., 1973) or the response to carotid occlusion (McGiff and Aviado, 1961), it was necessary to measure these variables as well as arterial pressure. To ensure a high degree of anatomical resolution we used stimulus conditions which probably limited spread of the stimulus current to distances no greater than 0.5 mm from the electrode tip. That this was the case was verified by the demonstration that moving the electrode tip 0.5 mm within an active zone could produce a very large increase in the size of the response, or its complete disappearance. Bagshaw and Evans (1976) also found with stimuli of comparable intensity (100 µA) the effective spread of current in brain was less than 0.5 mm.

By electrical stimulation we discovered that within the medulla oblongata of the rabbit there is an area from which hypertension and patterned regional vascular changes identical to those produced by ischemia can be elicited by low-intensity electrical stimulation. The area lies within the confines of a "pressor" area of the medulla which in turn appears to correspond in its principal distri-
bution to that of the pressor area defined in cats (Wang and Ranson, 1939; Alexander, 1946; Chai and Wang, 1962; Trouth et al., 1973). It extends from the level of the medial portion of the inferior olivary nucleus caudally to the level of entry of the facial nerve rostrally, a distance of about 6-7 mm. While not lying precisely within the confines of any single nucleus, it centers particularly on the nucleus reticularis parvocellularis and the dorsal part of the nucleus gigantocellularis. It is from the former nucleus that Trouth et al. (1973) reported that the most powerful pressor response can be elicited by focal electrical stimulation, from which Gootman and Cohen (1971) found the shortest latency between medullary stimulation and evoked potentials in the splanchic nerve, and into which baroreceptor afferents project (Miura and Reis, 1969). This active area also lies within the distribution of the central tegmental tract, a major associative pathway within the brainstem which contains ascending projections from brainstem noradrenergic neurons (Ungerstedt, 1971) and which is itself possibly of importance in cardiovascular control. Finally, this area corresponds to an area in the cat from which Doba and Reis (1972) found that focal distortion of neural tissue elicited a cardiovascular response very similar to the Cushing or cerebral ischemic response.

The response to electrical stimulation differed, however, in two respects from those produced by ischemia. First, the electrically elicited bradycardia differed from that elicited during ischemia in that it was entirely abolished by baroreceptor denervation, and thus was secondary to the rise of arterial pressure. Second, stimulation of this area increased rather than suppressed respiration, a finding comparable to that of Trouth et al. (1973) who stimulated homologous areas of the cat medulla. These findings suggest that no single receptive area exists in the medulla, which, when stimulated, triggers all components of the cerebral ischemic response. This is also strongly indicated by the fact that the vasomotor component of the naturally elicited response has a much shorter onset latency than either the vagal bradycardia or respiratory apnea. Thus, the restricted region of the medulla oblongata which mediates the vasomotor component of the ischemic response appears to differ from the regions responsible for the cardiovascular and respiratory components. This contention is supported by findings reported in the subsequent paper (Kumada et al., 1979) that lesions restricted to this vasomotor area abolish the vasomotor but not the respiratory or cardiovagal components of the naturally elicited reflex.

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### Table 6 Effect of Electrical Stimulation in Medullary Pressor Area on Cardiovascular Variables*

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Test</th>
<th>Difference</th>
<th>P value (control vs. test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>90.0 ± 10.5</td>
<td>164.6 ± 10.2</td>
<td>66.6 ± 3.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>296 ± 12</td>
<td>295 ± 17</td>
<td>9 ± 17</td>
<td>NS</td>
</tr>
<tr>
<td>Femoral flow (ml/min)</td>
<td>9.6 ± 0.5</td>
<td>8.9 ± 0.9</td>
<td>-1.6 ± 0.4</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Femoral vascular conductance (ml/min per mm Hg)</td>
<td>0.298 ± 0.006</td>
<td>0.048 ± 0.006</td>
<td>-0.050 ± 0.023</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Renal arterial flow (ml/min)</td>
<td>34.7 ± 2.8</td>
<td>31.5 ± 3.2</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Renal vascular conductance (ml/min per mm Hg)</td>
<td>0.393 ± 0.075</td>
<td>0.021 ± 0.011</td>
<td>-0.372 ± 0.067</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

* These data are all taken from seven rabbits in which the aortic nerves were transected. The data are expressed as mean ± SEM. NS = not significant (P > 0.05).
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