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

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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.

In the present study we have addressed ourselves to two questions concerning the central neural integration of the cerebral ischemic response. We have attempted to determine, in anesthetized rabbits, whether the response is elicited by stimulation of receptors outside of or within the brain, and which specific areas of the medulla oblongata are necessary for its expression.

This study was done in three parts. Initially, to produce baseline data for the subsequent investigations, we characterized the cardiovascular components of the response with respect to changes in regional distribution of blood flow, cardiac output, and their efferent mechanisms. In particular, we sought to determine for the first time whether the rise of arterial pressure elicited by ischemia secondarily influences the cardiovascular responses as a consequence of baroreceptor stimulation, and whether the response consists of patterned reproducible changes in blood flow through various vascular beds. By analyzing the effects on the response of baroreceptor denervation, we sought to distinguish between primary (occurring in the absence of baroreceptors) and secondary (modified by baroreceptors) responses. Next, by assessing the effects on the integrated response of various transections of brainstem and/or cranial nerves, we sought to...
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 transverse processes. Under a dissecting microscope, a hole about 2 mm in diameter was drilled with a dental burr through each transverse process of the 3rd vertebra into the cervical canal. A piece of cotton wool pasted with bone wax was forcefully inserted into each hole so as to completely occlude the vertebral arteries and veins. In most experiments, both carotid arteries were left open until just before an observation was made. Then, the left common carotid artery was clamped, and after about 1 minute later, cerebral ischemia was produced by clamping the right common carotid artery for a period of up to 1 minute. In other experiments, the left common carotid artery remained clamped throughout the experiment. The cerebral ischemic response was the same whether one or both carotid arteries remained open between periods of cerebral ischemia. Similarly, reversing the order in which the carotid arteries were clamped had no effect on the response. Under these conditions the responses were reproducible over many hours.

In preliminary experiments, it was established that only when the vertebral arteries were completely occluded, as verified by postmortem examination, could the highly characteristic pattern of the cerebral ischemic response (hypertension, bradycardia, and apnea) be produced by subsequent carotid clamping. Incomplete occlusion of any one of the vertebral or carotid arteries invariably resulted in failure to elicit the response.

All rabbits then were paralyzed with gallamine triethiodide (Flaxedil, Davis and Geek, Inc., 7 mg/kg im) and artificially ventilated with a mixture of 50% O2 and 50% N2, except for experiments in which respiratory changes were measured in spontaneously breathing rabbits. This was done to eliminate the secondary circulatory effects of systemic hypoxia associated with the reflex apnea elicited by cerebral ischemia. Up to the time when paralysis was induced, the adequacy of anesthesia was ascertained by the absence of reflex responses to painful stimuli. Urethane anesthesia in rabbits is highly stable and lasts for up to 24 hours (Westhues and Fritsch, 1965). The adequacy of anesthesia during the period when the rabbits were paralyzed was ensured by the fact that supplementary doses of urethane were not required in any of the experiments of equal or greater duration in nonparalyzed rabbits.

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 just below the inguinal ligament; (2) the left renal artery, approached retroperitoneally, with care taken to avoid damage to the renal nerves; (3) the superior mesenteric artery, approached through a 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 and superior mesenteric vascular beds were exposed, as described above, and denervated by sectioning the nerve bundles and nerve nets running along the respective arteries and in their immediate vicinity. The vagi were sectioned in the neck.

**Exposure of Brainstem**

The rabbit was placed in a rotating stereotaxic frame with the head flexed at 45°, and the brainstem was exposed by an occipital craniotomy. All cut edges of bone were sealed with bone wax.

**Brain Lesions and Cranial Nerve Section**

The brainstem was transected at various levels with a spatula. The spinal cord was transected at the C1 level by making a series of lesions with fine forceps under a dissecting microscope until the cord was completely transected. Cerebelllectomy was carried out by gentle aspiration of all cerebellar tissue. Cranial nerves IX, X, and XI were exposed by displacing the brainstem slightly and were then sectioned with fine scissors. Cranial nerves VII and VIII were transected with a sharp spatula at their point of entry into the cranium. The completeness of the transections was confirmed at the end of the experiments.

**Measurement of Cardiovascular and Respiratory Activity**

**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 cardi-otachometer (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).

**Regional blood flows** were recorded by either of two square-wave electromagnetic flow meters (Carolina Medical Electronics model 501, or Narco Bio-Systems 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.) bared 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...
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 ferrocyanide 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 = 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 vasocostriction 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;
FIGURE 1  (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>Variable</th>
<th>Baroreceptors intact</th>
<th>After aortic denervation</th>
<th>P value*</th>
<th>After sino-aortic denervation</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>n=10</td>
<td>104.7±2.3</td>
<td>102.0±2.3</td>
<td>NS</td>
<td>99.8±3.5</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>104.7±2.3</td>
<td>102.0±2.3</td>
<td>NS</td>
<td>99.8±3.5</td>
</tr>
<tr>
<td></td>
<td>Test</td>
<td>183.4±3.1</td>
<td>180.3±2.5</td>
<td>NS</td>
<td>176.9±5.6</td>
</tr>
<tr>
<td>Difference</td>
<td>78.7±2.5</td>
<td>78.3±2.3</td>
<td>NS</td>
<td>77.1±6.6</td>
<td>NS</td>
</tr>
<tr>
<td>P value‡</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>n=10</td>
<td>318±18</td>
<td>315±4</td>
<td>NS</td>
<td>278±13</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>318±18</td>
<td>315±4</td>
<td>NS</td>
<td>278±13</td>
</tr>
<tr>
<td></td>
<td>Test</td>
<td>171±18</td>
<td>280±7</td>
<td>&lt;0.001</td>
<td>231±17</td>
</tr>
<tr>
<td>Difference</td>
<td>−147±15</td>
<td>−35±6</td>
<td>&lt;0.001</td>
<td>−47±17</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>P value‡</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>AAF (ml/min)</td>
<td>n=4</td>
<td>293±29</td>
<td>296±29</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>293±29</td>
<td>296±29</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Test</td>
<td>126±21</td>
<td>122±15</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Difference</td>
<td>−167±15</td>
<td>−174±16</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>P value‡</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TPC (ml/min per mm Hg)</td>
<td>n=4</td>
<td>2.89±0.39</td>
<td>2.77±0.28</td>
<td>NS</td>
<td>2.77±0.28</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>2.89±0.39</td>
<td>2.77±0.28</td>
<td>NS</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>
<td>NS</td>
</tr>
<tr>
<td>Difference</td>
<td>−2.21±0.30</td>
<td>−2.12±0.23</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>P value‡</td>
<td>&lt;0.01</td>
<td>&lt;0.001</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 abolition 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. 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 adrenalectomy.

Thus, cerebral ischemia results in a differentiated pattern of peripheral vasoconstriction primarily mediated by sympathetic nerves. Although adrenomedullary 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></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<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>-0.051±0.006</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Denervated</td>
<td>11.7±1.1</td>
<td>23.1±2.2</td>
<td>11.4±1.9</td>
<td>&lt;0.01</td>
<td>0.111±0.10</td>
<td>0.153±0.014</td>
<td>0.042±0.012</td>
<td>&lt;0.06</td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>NS</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>NS</td>
</tr>
<tr>
<td>Mesenteric bed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact</td>
<td>63.8±10.8</td>
<td>54.6±10.4</td>
<td>-9.2±1.5</td>
<td>&lt;0.01</td>
<td>0.897±0.115</td>
<td>0.304±0.050</td>
<td>-0.593±0.066</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Denervated</td>
<td>80.3±16.5</td>
<td>101.6±29.8</td>
<td>21.2±14.6</td>
<td>NS</td>
<td>0.986±0.202</td>
<td>0.683±0.168</td>
<td>-0.302±0.056</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td>&lt;0.05</td>
<td>&lt;0.001</td>
<td>NS</td>
<td>&lt;0.06</td>
<td>NS</td>
<td>&lt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Renal bed</td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<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±0.063</td>
<td>&lt;0.06</td>
</tr>
<tr>
<td>Denervated</td>
<td>39.3±9.7</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±0.056</td>
<td>&lt;0.06</td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td>&lt;0.05</td>
<td>&lt;0.001</td>
<td>NS</td>
<td>&lt;0.06</td>
<td>NS</td>
<td>&lt;0.06</td>
<td>NS</td>
</tr>
</tbody>
</table>

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

entry of the facial nerves (which effectively interrupts inputs to the medulla of cranial nerves I-VIII) did not alter the magnitude of either the arterial pressure or heart rate responses (Table 4A, Fig. 3b), and in three spontaneously breathing animals did not abolish the apneic component of the response. However, in otherwise intact rabbits, transection of the spinal cord at C1 after brainstem transection virtually abolished the pressor response (Table 4B, Fig. 3e). Interestingly, spinal transection increased the magnitude of the vagally mediated reflex bradycardia (Table 4B, Fig. 3e), presumably due to interruption of outflow to cardiac sympathetics which were no longer opposing the action of the vagus. At the same time, the persistence of bradycardia in animals after spinal transection, despite the virtual abolition of the pressor response, further confirms that cerebral ischemia directly elicits bradycardia independently of baroreceptor reflexes.

These experiments demonstrate that the cardiovascular and, presumably, respiratory responses to cerebral ischemia are due to direct stimulation of neurons in the medulla oblongata.

Simulation of the Cerebral Ischemic Response by Focal Electrical Stimulation of the Medulla

Stimulus Frequency and Intensity Characteristics of the Region and Identification of Positive Points

In an initial survey in rabbits with intact baroreceptors, we observed that a rise of arterial pressure and bradycardia could be elicited by stimulation of the medulla oblongata.

TABLE 3

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

<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>Cardiac effentera intact</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>308±5</td>
<td>272±7</td>
<td>-36±6</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After vagotomy</td>
<td>18</td>
<td>296±9</td>
<td>32±6</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value (intact vs. vagotomized)</td>
<td>NS</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After vagotomy</td>
<td>7</td>
<td>214±8</td>
<td>221±8</td>
<td>7±2</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value (vagotomized vs. after vagotomy)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.05</td>
<td>NS</td>
<td></td>
<td></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>Lesion Description</th>
<th>n</th>
<th>Control (mean ± SE)</th>
<th>Test (mean ± SE)</th>
<th>Difference (mean ± SE)</th>
<th>P value (control vs. test)</th>
<th>Control (mean ± SE)</th>
<th>Test (mean ± SE)</th>
<th>Difference (mean ± SE)</th>
<th>P value (control vs. test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Effect of transection at the pontomedullary junction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact</td>
<td>8*</td>
<td>94.3 ± 3.3</td>
<td>174.5 ± 5.6</td>
<td>80.2 ± 5.2</td>
<td>&lt;0.001</td>
<td>315 ± 7</td>
<td>261 ± 31</td>
<td>−54 ± 22</td>
<td>NS</td>
</tr>
<tr>
<td>After pontomedullary transection</td>
<td></td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td></td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>P value (intact vs. transected)</td>
<td></td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td></td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>B. Effect of C1 spinal cord transection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact</td>
<td>6†</td>
<td>100.2 ± 2.5</td>
<td>179.2 ± 4.3</td>
<td>79.0 ± 5.8</td>
<td>&lt;0.001</td>
<td>310 ± 12</td>
<td>288 ± 17</td>
<td>−22 ± 15</td>
<td>NS</td>
</tr>
<tr>
<td>After C1 transection</td>
<td></td>
<td>NS</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
<td>NS</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P value (intact vs. transected)</td>
<td></td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td></td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>After subsequent vagotomy</td>
<td>3</td>
<td>97.0 ± 3.1</td>
<td>107.3 ± 4.7</td>
<td>10.3 ± 2.7</td>
<td>&lt;0.001</td>
<td>262 ± 23</td>
<td>264 ± 23</td>
<td>2 ± 1</td>
<td>NS</td>
</tr>
<tr>
<td>P value (transected vs. vagotomized)</td>
<td></td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td></td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>C. Effect of bilateral transection of cranial nerves IX-XI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact</td>
<td>3†</td>
<td>107.7 ± 4.3</td>
<td>181.7 ± 11.5</td>
<td>74.0 ± 7.5</td>
<td>&lt;0.05</td>
<td>300 ± 45</td>
<td>235 ± 65</td>
<td>−65 ± 20</td>
<td>NS</td>
</tr>
<tr>
<td>After transection of cranial nerves</td>
<td></td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td></td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>P value (intact vs. transected)</td>
<td></td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td></td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SE. NS = not significant (P > 0.05).
* In two of these experiments heart rate was not measured.
† In three of these experiments the brainstem had been previously transected at the pontomedullary junction.
‡ 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 Olczewski (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 4](http://circres.ahajournals.org/)

**Figure 4.** Elevation of arterial pressure and bradycardia elicited by electrical stimulation of the medulla. The upper panel represents a single electrode track penetrating the medulla oblongata. The stimulus was delivered at points 0.5 mm apart as marked on the diagram. The stimulus parameters in this and subsequent figures, unless otherwise specified, were: pulse duration, 0.5 msec; frequency, 50 Hz; amplitude, 100 μA. The lower panel illustrates arterial pressure and heart rate responses at each point. Note that the first change in arterial pressure is at point d but that a positive response (i.e., arterial pressure rise 50 mm Hg) was obtained only at points e and f. Abbreviations (for Figs. 4, 5, and 6): VII, facial nerve; Cn, nucleus cuneatus; Dvn, descending vestibular nucleus; Gn, nucleus gracilis; Lvn, lateral vestibular nucleus; Mvn, medial vestibular nucleus; N V, nucleus of trigeminal nerve; N VII, nucleus of facial nerve; N XII, nucleus of hypoglossal nerve; NmX, dorsal motor nucleus of vagus; Nts, nucleus of solitary tract; Oli, nucleus of the inferior olive; Ph, nucleus prepositus hypoglossi; Pyr, pyramidal tract; Rp, nucleus reticularis gigantocellularis; Rp, nucleus reticularis pontis; Rpc, nucleus reticularis parvocellularis; Tr sp V, spinal tract of the trigeminal nerve.)
ORGANIZATION OF CEREBRAL ISCHEMIC REFLEX/Dampney et al. 57

**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 bradycardias (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 stimulation (Fig. 8).

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.

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; Sagar 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

---

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

<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</td>
<td>Control</td>
</tr>
<tr>
<td>Baroreceptors intact</td>
<td>9*</td>
<td>102.9±1.7</td>
</tr>
<tr>
<td>After sino-aortic denervation</td>
<td>6†</td>
<td>102.3±6.5</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SEM. NS = not significant (P > 0.05).
* Bradycardia was not elicited in any of these rabbits.
† Bradycardia was the predominant response in seven of these nine rabbits.
vasoconstriction is primarily neurogenic and is mediated by α-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 β-receptor blockade, it probably is not neurogenic but possibly is due instead 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 β-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 Synder, 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-
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Electrical stimulation

- a) Upper panel: relationship between graded electrical stimulation of points in the medullary reticular area described in the text and elicited changes in mean arterial pressure (MAP) and femoral conductance (FC) (expressed as percent of control). Results taken from four rabbits. The stimulus intensity is expressed as multiples of threshold.

- Lower panel: relative changes in MAP and FC (expressed as percent of control) elicited by cerebral ischemia. Lower panel: relative changes in MAP and RC (expressed as percent of control) elicited by cerebral ischemia. Note similarity of changes in these parameters during electrical stimulation, over a wide range of stimulus intensities, particularly from 4 to 10 times threshold.

Brady...
Vagal bradycardia or respiratory apnea. Thus, the medulla, which, when stimulated, triggers all components of the cerebral ischemic response. This is also strongly indicated by the fact that the vaso-motor component of the naturally elicited response has a much shorter onset latency than either the vagal bradycardia or respiratory apnea. Thus, the

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

<table>
<thead>
<tr>
<th></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>Mean arterial pressure (mm Hg)</td>
<td>7</td>
<td>90.0 ± 10.5</td>
<td>164.6 ± 10.2</td>
<td>65.6 ± 3.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>7</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>4</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>4</td>
<td>0.058 ± 0.006</td>
<td>0.048 ± 0.006</td>
<td>-0.010 ± 0.023</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Renal arterial flow (ml/min)</td>
<td>3</td>
<td>34.7 ± 2.8</td>
<td>3.2 ± 1.3</td>
<td>-31.5 ± 3.2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Renal vascular conductance (ml/min per mm Hg)</td>
<td>3</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).

Reflex. 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 Trout 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

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