Effect of stimulation of the medullary reticular formation on cerebral vasomotor tonus and intracranial pressure

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The authors report the results of a study to evaluate the effect of stimulation of the medullary reticular formation on cerebral vasomotor tonus and intracranial pressure (ICP) after the hypothalamic dorsomedial nucleus and midbrain reticular formation were destroyed. Systemic arterial pressure (BP), ICP, and local cerebral blood volume (CBV) were continuously recorded in 32 cats. To assess the changes in the cerebral vasomotor tonus, the vasomotor index defined by the increase in ICP per unit change in BP was calculated. In 29 of the 32 animals, BP, ICP, and CBV increased simultaneously immediately after stimulation. The increase in ICP was not secondary to the increase in BP, because the vasomotor index during stimulation was significantly higher than the vasomotor index after administration of angiotensin II. The vasomotor index was high during stimulation of the area around the nucleus reticularis parvocellularis. In animals with the spinal cord transected at the C-2 vertebral level, ICP increased without a change in BP.

These findings indicate that the areas stimulated in the medullary reticular formation play an important role in decreasing cerebral vasomotor tonus. This effect was not influenced by bilateral superior cervical ganglionectomy, indicating that there is an intrinsic neural pathway that regulates cerebral vasomotor tonus directly. In three animals, marked biphasic or progressive increases in ICP up to 100 mm Hg were evoked by stimulation. The reduction of cerebral vasomotor tonus and concomitant vasopressor response induced by stimulation of the medullary reticular formation may be one of the causes of acute brain swelling.

KEY WORDS • intracranial pressure • reticular formation • cerebral vasomotor tonus • cerebral blood volume • cat

Typically, acute brain swelling is observed in patients with severe head injury, especially with acute subdural hematoma. Shortly after a subdural hematoma is removed, the brain may swell so massively that it protrudes through the craniotomy opening; this is associated with an increase in systemic arterial blood pressure (BP) and irregular respiration, indicating lower brain-stem dysfunction. Previous experimental and clinical studies have demonstrated that with acute brain swelling there is increased cerebral blood volume (CBV) secondary to disruption of metabolic and/or neurogenic control of cerebral vasomotor tonus. No definite therapy has been developed for acute brain swelling and its prognosis is still poor; thus, it is essential to analyze the pathogenesis of acute brain swelling.

Ishii experimentally produced acute brain swelling by destruction of the dorsomedial nucleus of the hypothalamus of monkeys. He assumed that one of the causes of acute brain swelling was a "release" of the caudal brain-stem facilitatory centers from rostral inhibitory control because of functional interruption of neural pathways in the upper brain stem. George reported that multiunit activity of the reticular formation of the medulla oblongata and red nucleus was initiated while activity of the more rostral structure (the lateral geniculate body) decreased during experimental intracranial hypertension. The present experiment was carried out to clarify the effect that stimulation of the medullary reticular formation has on cerebral vasomotor tonus and intracranial pressure (ICP).

The medullary reticular formation of cats was electrically stimulated under normal and elevated ICP after destruction of the dorsomedial nucleus of the hypothalamus and the reticular formation of the midbrain, both of which are reported to be rostral brain-stem vasomotor centers. During this time, continuous measurements of ICP and CBV were obtained. In order to identify the neural pathways of the medullary reticular formation that were acting on cerebral vasomotor tonus.
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tonus, electrical stimulation was performed in another group of cats after transection of the spinal cord at the C-2 vertebral level or after bilateral cervical ganglionectomy.

Materials and Methods

Animal Preparation

Experiments were conducted on 32 unselected cats, weighing between 3 to 4 kg each. Anesthesia was induced with intramuscular ketamine (30 mg/kg), and tracheostomy was performed. Anesthesia was then maintained with intravenous chloralose (70 mg/kg). The animals were paralyzed with pancuronium and maintained on a respirator while the arterial pCO$_2$ was kept between 30 and 35 mm Hg. Arterial pO$_2$ was examined intermittently with a blood gas analyzer and maintained at 80 to 110 mm Hg. The animals' temperature was regulated by a heat lamp at approximately 38°C. The femoral artery and vein were cannulated for measurement of BP by a pressure transducer and for the administration of drugs and Ringer's solution. The ICP was continuously measured with a plate-type pressure transducer placed in the right parietal epidural space.

The CBV was measured by a photoelectric method. The CBV sensor (7 mm in width, 15 mm in length, and 2 mm thick) was placed on the surface of the left parietal region through a burr hole. The CBV sensor was designed to measure the intensity of the optical absorption of hemoglobin in the brain tissue, and thus to indicate changes in CBV. The apparatus consisted of a 1-mm tungsten lamp and a photodiode covered with a filter. Silicone rubber was used to maintain the photodiode at a distance of 10 mm from the lamp. With this apparatus, qualitative changes in local CBV were continuously monitored. The BP, ICP, and outputs of the photodiode for CBV monitoring were also continuously recorded.

Brain-Stem Lesions

Upper brain-stem lesions were produced using monopolar electrode needles 0.8 mm in diameter. One electrode was inserted into both dorsomedial nuclei of the hypothalamus (at A 12.5, L ± 2.0, H -4.0) according to the atlas of Jasper and Ajmone-Marsan, and another was inserted into the reticular formation of the midbrain (at A 4.0, L ± 4.0, H 0) according to the atlas of Snider and Niemer. Electrocoagulation was performed at 3 mA for 1 minute. In addition, a concentric circular electrode connected to an electric stimulator was inserted bilaterally into the reticular formation of the medulla oblongata (at P 10, L ± 2.5, H -9.0) via small holes in the posterior fossa, in accordance with Snider and Niemer's atlas.

Animal Groups

The animals were divided into four groups. In Group A (eight animals), both dorsomedial nuclei of the hypothalamus and the reticular formation of the midbrain were destroyed. A transient ICP elevation was registered for 3 to 4 minutes, but thereafter the ICP became normal. In Group B (eight animals), after destruction of both dorsomedial nuclei of the hypothalamus and the reticular formation of the midbrain, 3 to 7 ml of autogenous blood was injected into the cisterna magna to produce acute subarachnoid hemorrhage (SAH), causing an elevation in the ICP of approximately 30 mm Hg. In Group C (eight animals), both superior cervical ganglia were resected immediately before the dorsomedial nuclei of the hypothalamus and the reticular formation of the midbrain were destroyed. To compensate for the hypotension resulting from cord transection, BP was maintained over 100 mm Hg by the continuous infusion of angiotensin II.

Experimental Protocol

In each group, the medullary reticular formation was stimulated electrically either uni- or bilaterally for 1 to 20 minutes. Stimulus parameters were nearly constant throughout most experiments: intensity 5 to 10 V, duration 1 msec, pulse-repetition frequency 10 to 50 pulses/sec. Stimulation was performed several times in one animal at intervals of at least 10 minutes. Immediately after starting stimulation, an elevation of BP and ICP was noted in all except for Group D animals.

To analyze the effect of stimulation of the medullary reticular formation on cerebral vasomotor tonus, we calculated the increase in ICP per unit change in mean arterial blood pressure (MABP); that is, ΔICP/ΔMABP (vasomotor index), as reported by Meyer, et al. A higher vasomotor index implies more impairment of autoregulatory capacitance or loss of cerebral vasomotor tonus. For that calculation, the change in the MABP at the time of the maximum change in the ICP was measured. Because the influence of an increase in BP on ICP and cerebral vasomotor tonus is appreciable, the vasomotor index was again calculated after angi-
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**FIG. 1.** Coronal brain sections showing (arrows): bilateral coagulated lesions of the hypothalamic dorso-medial nucleus (left) and midbrain reticular formation (center), and the sites of stimulation of the medullary reticular formation (right). Rule is metric.

Angiotensin II was injected intravenously to elevate the BP to the same level as at the time of stimulation of the reticular formation. At the termination of the experiments, the brain tissue at the tip of the stimulating electrode was coagulated in order to confirm the exact site of the electrode. The brains were removed and fixed in 10% formalin solution for 2 weeks, then sectioned in the coronal plane. Two-group comparisons were evaluated with Student's unpaired t-test.

**Results**

The coagulated lesions of the bilateral dorsomedial nuclei of the hypothalamus and reticular formation of the midbrain and the sites of stimulation of the medulla oblongata in one animal are shown in Fig. 1. The lesions were approximately 1.0 mm in diameter, and the stimulation sites were mostly located in the paramedian reticular formation of the medulla oblongata.

In 29 of the 32 animals representing all four groups, temporary ICP elevation of 2 to 36 mm Hg was observed after stimulation of the medullary reticular formation. A concomitant increase in CBV and BP was recorded during stimulation of the medullary reticular formation in the animals with normal ICP (Group A), increased ICP (Group B), and cervical ganglionectomy (Group C) (Fig. 2). The changes in BP, ICP, and CBV following stimulation were essentially the same among these three groups: BP, ICP, and CBV increased simultaneously immediately after stimulation, although there was a dissociation of changes in BP and ICP. The BP rose gradually and remained elevated during stimulation. On the other hand, ICP increased abruptly 1 to 3 seconds after stimulation, reaching a maximum level within 30 seconds following the start of stimulation. It then fell gradually, presumably due to intracranial spatial compensation of displaceable fluid. The CBV started to increase immediately after stimulation of the reticular formation and remained elevated during stimulation.

When angiotensin II was administered, the ICP rose simultaneously with the abrupt increase in BP. However, in spite of the fact that BP elevation was of the same degree after angiotensin II administration and stimulation of the reticular formation, the increase in

![Fig. 2. Changes in mean systemic arterial blood pressure (ΔBP), intracranial pressure (ΔICP), and local cerebral blood volume (CBV) during stimulation of the medullary reticular formation (MORF) and after administration of angiotensin II in the animals with normal ICP, increased ICP, and bilateral superior cervical ganglionectomy.](image)
ICP after angiotensin II administration was less in all cases. In the animals with C-2 cord transection (Group D), no consistent changes in BP were observed during stimulation of the reticular formation. However, the ICP rose immediately after stimulation simultaneously with the increase in CBV, irrespective of the reaction of BP (Fig. 3 and Table 1).

Table 1 shows the changes in ICP (ΔICP) and BP (ΔBP) and vasomotor index (ΔICP/ΔBP) in each group after angiotensin II administration and stimulation of the reticular formation. The vasomotor index is given for Groups A, B, and C in Fig. 4. In Groups A and C (with normal ICP and normal ICP with cervical ganglionectomy, respectively), there was no significant difference in ΔBP between the groups with angiotensin II administration and stimulation of the reticular formation, whereas, in Group B (with increased ICP), the increase in ΔBP with stimulation of the reticular formation was significantly lower than in the animals with administration of angiotensin II. However, in Groups A, B, and C, the ICP and vasomotor index were significantly higher in all animals with stimulation of the medullary reticular formation, indicating more severe impairment of autoregulatory capacitance of the cerebral vessels.18 In Group B (with increased ICP), the vasomotor index after angiotensin II administration and during stimulation of the reticular formation showed significantly higher values than in Group A due to a decrease in intracranial compliance. In each group, changes in ICP and vasomotor index showed no significant difference between unilateral and bilateral stimulation.

Figure 5 shows the positions of the electrode tip for stimulation of the medullary reticular formation in Groups A, B, and C. The sites yielding vasomotor

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**TABLE 1**

<table>
<thead>
<tr>
<th>Group &amp; Protocol</th>
<th>No. of Tests</th>
<th>ΔICP (mm Hg)</th>
<th>ΔBP (mm Hg)</th>
<th>ΔICP/ΔBP</th>
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<tbody>
<tr>
<td>Group A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>angiotensin II</td>
<td>8</td>
<td>2.6±1.3</td>
<td>61±19</td>
<td>0.04±0.01</td>
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<tr>
<td>unilat. or bilat.</td>
<td>16</td>
<td>10.5±6.1†</td>
<td>67±20</td>
<td>0.16±0.08+</td>
</tr>
<tr>
<td>MORF stim.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group B</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>angiotensin II</td>
<td>17</td>
<td>6.4±5.0†</td>
<td>66±27</td>
<td>0.09±0.06‡</td>
</tr>
<tr>
<td>unilat. MORF stim.</td>
<td>25</td>
<td>13.8±9.9†‡</td>
<td>35±20‡</td>
<td>0.43±0.22†‡</td>
</tr>
<tr>
<td>bilat. MORF stim.</td>
<td>13</td>
<td>17.5±9.9†‡</td>
<td>40±22†‡</td>
<td>0.47±0.17†‡</td>
</tr>
<tr>
<td>Group C</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>angiotensin II</td>
<td>16</td>
<td>3.9±1.7</td>
<td>50±17</td>
<td>0.09±0.05‡</td>
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<tr>
<td>unilat. MORF stim.</td>
<td>45</td>
<td>10.1±9.0†‡</td>
<td>47±24†‡</td>
<td>0.22±0.16†‡</td>
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<td>bilat. MORF stim.</td>
<td>15</td>
<td>12.9±10.7†‡</td>
<td>55±21†‡</td>
<td>0.24±0.14†‡</td>
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<td>Group D</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>angiotensin II</td>
<td>15</td>
<td>3.9±3.2</td>
<td>52±18</td>
<td>0.07±0.05</td>
</tr>
<tr>
<td>unilat. or bilat.</td>
<td>57</td>
<td>5.2±4.7†‡</td>
<td>ND</td>
<td>ND</td>
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<tr>
<td>MORF stim.</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>decrease in BP</td>
<td>16</td>
<td>2.8±1.6†</td>
<td>-14±9‡</td>
<td>ND</td>
</tr>
<tr>
<td>no change in BP</td>
<td>20</td>
<td>5.6±4.9†‡</td>
<td>0†‡</td>
<td>ND</td>
</tr>
<tr>
<td>increase in BP</td>
<td>21</td>
<td>7.0±5.3†</td>
<td>18±11†‡</td>
<td>0.50±0.73†‡</td>
</tr>
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</table>

* Changes in intracranial pressure (ΔICP), systemic arterial pressure (ΔBP), and vasomotor index (ΔICP/ΔBP) after administration of angiotensin II and stimulation of the medullary reticular formation (MORF) in Group A (normal ICP), Group B (increased ICP), Group C (cervical ganglionectomy), and Group D (transection of the spinal cord at C-2). ND = not done. BP = blood pressure.
† Value significantly different (p < 0.05 or more) from that of animals with angiotensin II administration.
‡ Value significantly different (p < 0.05 or more) from that of animals with normal ICP.
§ Value significantly different (p < 0.05 or more) from that of animals with normal ICP.

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**Fig. 3.** Representative changes in mean systemic arterial blood pressure (ΔBP), intracranial pressure (ΔICP), and local cerebral blood volume (CBV) during stimulation of the medullary reticular formation (MORF) in a Group D animal (with transection of the spinal cord at C-2).
FIG. 5. The positions of the electrode tip used to stimulate the medullary reticular formation are indicated by enclosed areas. The regions that showed a higher vasomotor index are illustrated on the left side. See text for explanation. N.R. = nucleus reticularis.

FIG. 6. Abrupt, high elevation of intracranial pressure (ICP) was repeatedly evoked by stimulation of the medullary reticular formation in one animal in Group B in which the ICP was already increased by subarachnoid hemorrhage. Four separate tracings are shown. BP = systemic arterial blood pressure.

indexes above the mean value are indicated on the left side, and those below the mean value are on the right side. The vasomotor index was high during stimulation of the reticular formation medial to the tegmentum of the medulla oblongata; that is, the region extending from the nucleus reticularis parvocellularis to the nucleus reticularis gigantocellularis. In three of the 32 animals (one in Group B and two in Group C), a biphasic or progressive increase in ICP was observed during stimulation of the medullary reticular formation. In one Group B animal, ICP increased above 30 mm Hg after injection of blood into the cisterna magna. Stimulation of the reticular formation in all four different groups invariably induced an abrupt increase in ICP up to 40 to 70 mm Hg, then the ICP continued to rise biphasically to 100 mm Hg during stimulation. The ICP promptly decreased after cessation of the stimulation (Fig. 6).

Figure 7 illustrates the results of another experimental manipulation in Group C. After resection of the bilateral superior cervical ganglion and bilateral destruction of the dorsomedial nucleus of the hypothalamus and reticular formation of the midbrain, the unilateral reticular formation of the medulla oblongata was stimulated. The BP rose to and remained at approximately 30 mm Hg after stimulation. The ICP gradually increased to about 70 mm Hg 14 minutes after the start of stimulation. With discontinuation of stimulation, the ICP declined. At autopsy, there was no hematoma, and the tip of the stimulating needle in all three animals was located in the region around the nucleus reticularis parvocellularis, corresponding to the region mentioned before where a transient ICP elevation was obtained.

Discussion

Acute brain swelling has been experimentally induced by producing lesions in the diencephalon and brain stem, including the floor of the fourth ventricle and the medulla,20 the dorsomedial nucleus of the hypothalamus7 and area preoptica, the nucleus supraopticus, the nucleus ruber, the thalamus, the tegmental reticular formation, and the substantia nigra.24 Loss of cerebral vasomotor tonus with an increase in CBV secondary to disruption of neurogenic control has
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been considered as a possible reason for the rapid development of brain swelling shortly after the lesion is produced. Stimulation of the brain stem also influences the cerebral vasomotor tonus. Langfitt and Kassell14 studied the effect of brain-stem stimulation on cerebral blood flow (CBF) measured with electromagnetic flowmeters placed on the common carotid arteries and found that cerebral vasodilatation produced by stimulation of the brain stem is most likely of neurogenic origin.

With regard to stimulation of the brain-stem reticular formation, Ingvar and Söderberg6 showed that stimulation produced electroencephalography (EEG) desynchronization and a relative increase in CBF as indicated by a cerebral venous drip recorder. Meyer, et al.,17 reported that during stimulation of the pontine reticular formation, CBF and oxygen consumption usually increased if the EEG showed desynchronization. They presumed that the increase in CBF was caused by increased cerebral metabolism associated with EEG desynchronization. On the contrary, Molnár and Szántó19 studied the effect of stimulation of the medullary vasomotor center on EEG and CBF and found that changes in blood flow were not related consistently to EEG patterns; they concluded that a center in the medulla exerts a specific effect on cerebral vessels independent of the EEG and cerebral metabolism. Recently, stimulation of a restricted area of the dorsal medullary reticular formation (the border zone between the nuclei parvocellularis and gigantocellularis dorsalis) has been demonstrated to elicit a widespread significant increase in CBF, especially in the cerebral cortex, and to abolish autoregulation, which is closely coupled to a parallel increase in cerebral metabolism.2,22 The effect appears to be mediated by intrinsic pathways of the central nervous system because the increase in CBF evoked by stimulation persists after transection of the spinal cord or cervical sympathetic trunk.5

These experimental data seem to show that lesions of the rostral vasomotor center of the brain stem and stimulation of the medullary reticular formation both result in loss of cerebral vasomotor tonus and a consequent increase in CBF and ICP. In fact, in patients with acute brain swelling, brain-stem lesions are frequently demonstrated on computerized tomography3,5 or revealed at autopsy.16 In our experimental model, electrical stimulation of the medullary reticular formation was employed after lesions were made in the hypothalamus and midbrain. With stimulation of the medullary reticular formation, an abrupt increase in BP up to 100 mm Hg was invariably observed except in Group D. Because the marked increase in BP secondary to stimulation should be considered to have some influence on cerebral vasomotor tonus,11 the vasomotor index was employed to assess the changes in cerebral vasomotor tonus that Meyer, et al.,18 termed “autoregulatory capacitance.” In this experiment, animals were immobilized and mechanically ventilated, and arterial blood gases and pH were maintained within the normal range. Thus, changes in blood gas and pH levels did not contribute to the changes in cerebral vasomotor tonus produced by brain-stem stimulation.

In the case of medullary stimulation, the elevation of BP was nearly equal to that after angiotensin II administration. Nevertheless, the ICP rose more with the increase in CBV, and the vasomotor index showed a significantly higher value than that after angiotensin II administration. In addition to the vasopressor response, two-thirds of the animals with cervical transection (Group D) that underwent stimulation showed no change or a decrease in BP. The exact mechanism is hard to explain in this experimental model. However, medullary stimulation invariably caused increases in ICP and CBV. These data clearly support the hypothesis that stimulation of the medullary reticular formation directly decreased the cerebral vasomotor tonus and increased CBV and ICP. During stimulation, an elevation of ICP in Group D animals (with cervical cord transection) was significantly lower than in the other three groups. This result shows that the increase in BP with medullary stimulation also plays a role in the acute increase of ICP. In the animals with increased ICP (Group B), the vasomotor index of medullary stimulation was significantly higher than that of the animals with normal ICP (Group A). Thus, under the condition of increased ICP with decreased intracranial compliance, stimulation of the medullary reticular formation may result in further elevation of ICP secondary to decreased cerebral vasomotor tonus and increased BP. A high vasomotor index was found in the medullary reticular formation during stimulation of the nucleus reticularis parvocellularis and gigantocellularis, indicating that this is an essential area of medullary cerebral vasomotor control. Molnár and Szántó19 and Iadecola, et al.,5 reported that the increase in CBF evoked by stimulation of the medullary reticular formation persisted after transection of the spinal cord5 or cervical sympathetic trunk; they concluded that the effect was mediated by intrinsic pathways of the central nervous system acting directly on the cerebral vessels. Our data also show that cerebral vasomotor tonus was significantly affected by medullary stimulation even after transection of the spinal cord or cervical ganglion; this finding supported the concept of ascending intracerebral pathways that originate or pass through the medullary reticular formation and act on the cerebral vessels.

In three of the 32 animals, marked biphasic or progressive increases in ICP were evoked during stimulation of the medullary reticular formation; these peaks were similar to a plateau wave of acute brain swelling. In these three animals, the preparation of animals, stimulation conditions, and location of the stimulating electrode were essentially the same as in the animals that showed a small temporary increase in ICP after medullary stimulation. We believe the findings warrant further investigation of the exact mechanisms of the two different response patterns of ICP. The region of
the parvocellular and gigantocellular reticular nuclei appears to play a critical role in mediating the Cushing vasopressor response. In critical intracranial hypertension, excitation of the above region has a high probability of inducing further increases in ICP secondary to loss of the cerebral vasomotor tonus via intrinsic pathways and vasopressor response, consequently resulting in acute brain swelling. The Cushing response seems to be one of the factors in the vicious circle leading to acute brain swelling, so that stabilization of the medullary reticular formation may become a useful therapeutic maneuver for acute brain swelling.

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References


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