Role of the medulla oblongata in plateau-wave development in dogs

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Plateau waves reflect both dilatation of the cerebral vessels and an increase in the cerebral blood volume under increased intracranial pressure (ICP). They are often associated with changes in arterial blood pressure (BP) and respiration, suggesting a role of the brain stem in their development. In experiments conducted on dogs in which intracranial hypertension was induced by occluding the neck veins, the authors stimulated the brain-stem reticular formation in the medulla oblongata and caudal pons to identify the brain sites that produce plateau-like responses. A rise in ICP was observed following stimulation of most areas of the brain stem and was associated with changes in arterial BP, cerebral perfusion pressure (CPP), cerebral blood flow (CBF), respiration, and pulse rate. The stimuli delivered to the medial reticular formation of the caudal medulla caused an arterial depressor response, a decrease in CPP and CBF, suppressed ventilation, and bradycardia; these responses were similar in many respects to plateau waves observed in clinical practice and almost corresponded to the depressor region of the vasomotor center. It is hypothesized that the medullary depressor area may play a role in eliciting cerebral vasomotor reaction concerned with the development of plateau waves in a state of increased ICP.

KEY WORDS: plateau waves · medulla oblongata · intracranial pressure · cerebral perfusion · dog

Plateau waves, as described by Lundberg, are often observed in patients with increased intracranial pressure (ICP) due to brain tumors, benign intracranial hypertension, hydrocephalus, superior sagittal sinus thrombosis, and other conditions. Typical plateau waves are characterized by a sudden increase in ICP to values of 50 to 100 mm Hg, continuation of this pressure for a period of time (usually 5 to 20 minutes), and then a rapid fall to the original level or below.

Two major causes have been proposed for the development of plateau waves: persistent intracranial hypertension and a cerebral vasomotor reaction. With regards to the first factor, it has been suggested that, when the ICP is on the steep part of the pressure/volume curve, compliance in the cranial cavity may be reduced and changes in the intracranial dynamics that cause a rise in ICP may elicit an enhanced secondary rise in ICP. Concerning the second factor, it has been shown that a plateau wave is accompanied by an increase in cerebral blood volume (CBV) resulting from dilatation of the resistant cerebral vessels and at the same time the cerebral blood flow (CBF) decreases.

Changes in arterial blood pressure (BP), cerebral perfusion pressure (CPP), respiration, and pulse rate are known to occur during plateau waves. Except for the CPP changes, these associated signs suggest that the brain stem may play a role in the development of the waves.

We induced intracranial hypertension in dogs by occluding the neck veins, then stimulated the brain-stem reticular formation in the medulla oblongata and the pons to produce changes in the arterial BP, CPP, respiration, CBF, and pulse rate similar to those associated with plateau waves. Our objective was to identify brain sites that cause the cerebral vasomotor reaction responsible for the development of plateau waves.

Materials and Methods

Animal Preparation

Twenty adult mongrel dogs of both sexes, weighing 7 to 10 kg each, were used in this study. All animals were cared for in accordance with the guidelines of the Japan Science Council on Animal Experimentation. The animals were anesthetized with intramuscular ketamine hydrochloride, 10 mg/kg, and intravenous thio-
pental sodium, 5 mg/kg; in addition, 2 to 3 mg/kg of thiopental sodium was given as necessary. The dogs were then tracheotomized, and the experiments were carried out under spontaneous breathing. Rectal temperature was monitored continuously, and an attempt was made to maintain it at 37° ± 1°C (mean ± standard deviation) by the use of a heating blanket. A femoral vein was catheterized for the administration of medications and maintenance saline solution.

**Recording Physiological Parameters**

The ICP was recorded through a No. 16 needle, which was inserted into the lateral ventricle and connected to a pressure transducer.* To monitor the arterial BP and for periodic sampling of blood gases, a catheter was placed into the abdominal aorta via the femoral artery. The CPP was expressed as the difference between the arterial BP and the ICP. The rate and mode of respiration were recorded using a thermistor bridge applied to the tracheostomy opening.

**Measurement of Cerebral Blood Flow**

Cortical CBF was measured continuously with a temperature-controlled thermoelectric method using a tissue blood flow monitor.† The probe of this apparatus consisted of two gold plates, of which one acts as a microheater and the other as a reference. The difference in temperature between the two plates is always kept at 2°C by a self-controlled system, and the heating power of the microheater used to maintain a constant temperature indicated the rate of CBF. The probe was placed on the surface of the parietal cortex through a burr hole. The thermoelectric flowmeter was calibrated prior to the experiments by a hydrogen clearance method. Thus, an absolute CBF value could be obtained continuously throughout the experiments.

**Placement of Measurement and Stimulation Devices**

The animal was positioned prone with the head elevated and fixed in a stereotaxic frame. The calvaria was exposed and burr holes were made with a high-speed drill for placement of a cannula for monitoring ICP, a probe for measuring the cortical CBF, and a bipolar electrode for brain-stem stimulation. Placement of the cannula in the lateral ventricle and of the bipolar electrode at the desired brain sites was achieved under stereotaxic guidance according to the technique of Lim, et al. 17 Following placement of the devices, the burr holes were sealed with dental acrylic and adhesive, with care being taken not to let cerebrospinal fluid (CSF) leak from the holes, because this may result in misleading ICP recordings.

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* Pressure transducer, Model P-50, manufactured by Gould Statham, Inc., Oxnard, California.
† Tissue blood flow monitor, Model UMW-101, manufactured by Unique Medical Co., Ltd., Tokyo, Japan.

**Electrical Stimulation**

The area of the brain stem that was chosen for stimulation lay between the caudal pons and the medulla oblongata (Fig. 1). Stimulation was effected by a train of electrical pulses produced with the bipolar electrode, which was made from Teflon-coated stainless steel tubing (outer diameter 500 μ) inserted into two Teflon-coated tungsten filaments (each 125 μ in diameter). The electrode tips were bare to a length of 200 μ, and were placed 1 mm apart. The electrical pulses were delivered by a stimulator through a stimulus isolation unit. At the beginning of each experiment the pulse duration and frequency were set at 1 msec and 50 Hz, respectively, in order to obtain the threshold for stimulation, and the current intensity was increased from 0.1 to 1 mA until optimal arterial BP and ICP responses were achieved for each animal. Duration of the stimulus was usually between 10 and 15 seconds. In experiments involving stimulation of the medullary reticular formation in rats, Iadecola, et al., 10 noted that when stimulus frequency was varied at a stimulus intensity of a certain level the effect of the stimulation on the arterial BP appeared at 2 Hz, was almost maximal at 50 Hz, and reached a maximum level between 100 and 300 Hz. In our present study in dogs, a stimulus frequency of 50 Hz was chosen in order to obtain nearly maximal responses of arterial BP and ICP at the lowest possible stimulation frequency.

**Occlusion of Neck Veins**

The neck veins were occluded bilaterally with thread at the C-4 vertebral level so as to induce persistent intracranial venous hypertension. The vessels ligated included the bilateral external and internal jugular veins, bilateral caudal thyroid veins, and superficial cervical veins. The mean ICP was 9 ± 2 mm Hg prior to the occlusion of the neck veins, and 32 ± 6 mm Hg after occlusion.

**Autopsy Studies**

After completion of the experiments, the animals were killed by intravenous injection of a large dose of thiopental sodium followed by KCl. Autopsies were performed for confirmation of the needle site in the brain stem. Microscopic sections were embedded in celloidin and stained with the hematoxylin and eosin and Nissl methods.

**Results**

Stimulation of most areas of the brain-stem reticular formation in the medulla and pons always produced an ICP increase associated with changes in arterial BP, CPP, CBF, respiration, and pulse rate. The amplitude of the ICP increase was 15 to 32 mm Hg (mean 21 mm Hg) and the duration was 80 to 186 seconds (mean 116...
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FIG. 2. Tracings showing Response 1 evoked by stimulation of the lateral reticular formation in the rostral medulla in a dog in which electrical stimulation (STIM, 0.5 mA, 1 msec, 50 Hz) was applied for 15 seconds. ABP = arterial blood pressure; ICP = intracranial pressure; CPP = cerebral perfusion pressure; resp = respiration; CBF = cerebral blood flow.

FIG. 3. Tracings showing Response 2 evoked by stimulation of the medial reticular formation in the caudal medulla in a dog in which electrical stimulation (STIM, 0.5 mA, 1 msec, 50 Hz) was applied for 10 seconds. ABP = arterial blood pressure; ICP = intracranial pressure; CPP = cerebral perfusion pressure; resp = respiration; CBF = cerebral blood flow.

FIG. 1. Diagram showing the areas of the brain stem stimulated in 20 dogs. Each circle in A represents one animal. Open circles indicate the points that produced Response 1 shown in Fig. 2. Solid circles indicate the points that produced Response 2 shown in Fig. 3. A: Dorsal surface of the brain stem. B-F: Cross sections through the medulla and the pons at levels indicated by guidelines to A. Abbreviations: CC = canalis centralis; CI = colliculus superior; FC = fasciculus cuneatus; FG = fasciculus gracilis; NC = nucleus cuneatus; NG = nucleus gracilis; NLL = nucleus lemnisci lateralis; NOI = nucleus olivaris inferior; NOS = nucleus olivaris superior; NR = nuclei raphes; PCI = pedunculus cerebellaris inferior; PCM = pedunculus cerebellaris medius; PCS = pedunculus cerebellaris superior; PMO = pyramis medullae oblongatae; TS = tractus solitarius; TSNT = tractus spinalis nervi trigemini; V and VIII = corresponding cranial nerves.

The changes were divided into two groups. One group (Response 1) comprised those changes indicating an arterial pressor response, increases of CPP and CBF, hyperventilation, and bradycardia (Fig. 2), and the other group (Response 2) included those changes showing an arterial depressor response, decreases of CPP and CBF, depressed ventilation, and bradycardia (Fig. 3). In Response 1 the respective changes in arterial BP, CPP, and CBF ranged from 42 to 68 mm Hg (mean 50 mm Hg), 20 to 32 mm Hg (mean 28 mm Hg), and 10 to 25 ml/100 gm/min (mean 19 ml/100 gm/min); in Response 2 they ranged from 32 to 60 mm Hg (mean 48 mm Hg), 20 to 38 mm Hg (mean 28 mm Hg), and 12 to 26 ml/100 gm/min (mean 18 ml/100 gm/min). Of these changes, Response 2 shared similarities with the plateau waves observed in clinical practice, except for the amplitude of the ICP increase.

The stimulus points in the brain stem that produced Responses 1 and 2 are shown in Fig. 1. Response 1
usually resulted from stimulation of a region of the lateral reticular formation in the rostral medulla and caudal pons, and this area almost corresponded to the depressor area of the vasomotor center. On the other hand, Response 2 resulted from the stimulation of the medial reticular formation in the caudal medulla, and this region almost corresponded to the depressor area of the vasomotor center. These reports, it seems certain that a decline or little increase is of only moderate magnitude. If the increase is of only moderate magnitude: The increase is accompanied by decreases of CPP and CBF. The changes were divided into two groups: the arterial pressor response associated with changes in arterial BP, CPP, and CBF, as well as an increase in ICP. We suggest that the depressor area of the vasomotor center may play a role in eliciting cerebral vasomotor reaction for the development of plateau waves in a state of intracranial hypertension.

Discussion

Lundberg, et al., claimed that plateau waves pertain to an intermediate stage in the progress of intracranial hypertension, when the facility for spatial compensation has been depleted. Clinically, plateau waves develop most frequently in patients with an elevated baseline pressure ranging from 20 to 40 mm Hg. In the present study, the dogs' ICP was elevated by occluding the neck veins causing intracranial venous hypertension, and the experiments were carried out under a moderately increased ICP of about 32 mm Hg.

Clinical observations suggest that the appearance of plateau waves is a sign of decreased CSF absorption, causing a tight condition within the cranial cavity. It has also been indicated that this tight condition may elicit a secondary rise of ICP (a plateau wave) in response to any change in the intracranial dynamics, even if the increase is of only moderate magnitude. Lundberg, et al., suggested that the plateau-wave phenomenon is related to a cerebral vasomotor response; that is, to a dilatation of resistant cerebral vessels during a state of decreased compliance in the cranial cavity.

Langfitt and Kassel observed that stimulation of the brain stem produced both dilatation of the cerebral vessels and a rise in ICP. It has been reported that there is abundant autonomic nerve supply to the cerebral arteries and recently, clear evidence has been found that some of these fibers are derived from the brain stem. These reports suggest that the tone and reactivity of the cerebral arteries may change in accordance with the intrinsic activity of the brain stem and may elicit variations in ICP, arterial BP, and CBF. In the present study, we found that the rise in ICP produced by stimulation of the brain-stem reticular formation was accompanied by changes in arterial BP, CPP, and CBF. The changes were divided into two groups: the arterial pressor response associated with increases of CPP and CBF, and the arterial depressor response accompanied by decreases of CPP and CBF.

Clinical observations suggest that plateau waves occur irrespective of variations in arterial BP resulting in a marked reduction in CPP. However, in their laboratory studies Rosner and Becker found that plateau waves are not independent of systemic circulatory events; that is, a gradual decline in arterial BP occurs at the beginning of and during plateau waves. From these reports, it seems certain that a decline or little change in arterial BP is a characteristic of the plateau-wave phenomenon, and that the phenomenon is never accompanied by a rise in the arterial BP. It has been reported that CBF during plateau waves was decreased compared with measurements made during the intervals between two such waves. Also, angiograms obtained during plateau waves have shown wider vessels in the arterial phase than during the interval phase between two plateau waves.

The inspiratory and expiratory fields of the respiratory center are located in the reticular formation of the caudal medulla, and stimulation of these fields results in apneusis. Clinically, plateau waves develop in intimate relationship to respiratory alterations, suggesting the role of the medulla in their development.

Different respiratory alterations are known to occur during plateau waves, with suppressed respiration being the most common. A decrease in the pulse rate is also observed at the beginning of the waves and continues during and for some time after the waves, also suggesting brain-stem dysfunction.

In our present study, the brain-stem reticular formation in the medulla oblongata and the caudal pons was stimulated extensively and always produced an ICP increase associated with changes in arterial BP, CPP, CBF, respiration, and pulse rate. Responses to the stimuli were grouped into two types. Of these two types, Response 2, which was evoked by stimulation of the medial reticular formation of the caudal medulla, was similar in many respects to the plateau waves observed in clinical practice, except for the amplitude of the ICP increase. These similarities included a decline in arterial BP, CPP, and CBF, respiratory suppression, and bradycardia, as well as an increase in ICP. We suggest that the depressor area of the vasomotor center may play a role in eliciting cerebral vasomotor reaction for the development of plateau waves in a state of intracranial hypertension.

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