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The Effects of Local Intraparenchymal Pentobarbital on Intracranial Hypertension Following Experimental Subarachnoid Hemorrhage

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Barbiturates are often utilized clinically in circumstances in which elevated intracranial pressure is expected. In this study, the mechanism of action of barbiturates was examined in dogs with intracranial hypertension induced by injecting autogenous incubated blood into the chiasmatic cistern. Intracranial pressure and systemic blood pressure were continuously monitored. A single bilateral administration of powdered pentobarbital (2 mg and 0.4 mg) in experimental animals and solid d-glucose (2 mg) in control animals was given into the posterior hypothalamus, pontine reticular formation, or medullary reticular formation when intracranial pressure reached 20–30 mmHg after the blood injection—usually in 3–6 h. The increased intracranial pressure following the experimental subarachnoid hemorrhage was always associated with either intracranial pressure irregularities or concomitant blood pressure variations, suggesting the presence of vasomotor instability. Administration of both 2 mg and 0.4 mg of pentobarbital into the medulla caused a significant ($P < 0.01$) decrease of the intracranial pressure to 44 and 65% of control and stabilization of the intracranial pressure irregularities, whereas pentobarbital given at the other sites did not. The blood pressure was also decreased significantly ($P < 0.01$) to 80 and 88% of control and the blood pressure variations were stabilized in animals after administration of pentobarbital into the medulla, whereas in those given pentobarbital at the other sites, it was not. The results suggest that, in the presence of elevated intracranial pressure following experimental subarachnoid hemorrhage, the mechanisms of action of barbiturates in reducing the intracranial pressure may result from alleviation of cerebral vasomotor instability by depression of the vasomotor center of the medulla. (Key words: Anesthetics, intravenous: pentobarbital. Brain: intracranial hypertension; intracranial pressure; subarachnoid hemorrhage; vasomotor center; vasomotor instability.)

THE USEFULNESS OF barbiturates in reducing the intracranial pressure (ICP) in patients with head injury, cerebral hemorrhage, Reye's syndrome, and other non-traumatic lesions is widely accepted.[1-5] It has been suggested that the decline in ICP is due to the reduction in cerebral blood volume caused by the direct constrictive effect of barbiturates,[2,4,6,7] and that the decreased neural metabolic rates caused by the barbiturates lead to a decrease in the cerebral blood flow, resulting in a reduction of the increased ICP.[8-10] The mechanism of barbiturate-induced ICP reduction, however, has not yet been fully elucidated, but it is probably multifactorial.[11] Barbiturates produce a general depression of the central nervous system, and, because of nonspecificity of their action, it is impossible to achieve the desired effect without evidence of this general depression.[10,12]

Clinically, subarachnoid hemorrhage (SAH) is often accompanied by increased ICP,[13,14] showing marked spontaneous fluctuations or oscillating waves synchronous with the arterial pulse, and it is suggested that the cerebral vasodilatation due to vasomotor instability might be a cause of the increased ICP.[14]

In this study, we applied pentobarbital locally into subcortical brain sites in dogs with intracranial hypertension following experimental SAH in an attempt to analyze the mechanisms of action of barbiturates on increased ICP.

Materials and Methods

PREPARATION OF ANIMALS

Sixty-one adult mongrel dogs of either sex (7–12 kg) were the subjects of this study. All animals were cared for in accordance with the Recommendation of the Japan Science Council on Animal Experiment Guidelines. The animals were anesthetized with intramuscular ketamine hydrochloride and paralyzed with intravenous gallamine triethiode. The initial doses were 15 and 1.5 mg/kg, and the maintenance dosages were 10 and 1 $mg \cdot kg^{-1} \cdot h^{-1}$, respectively. Following tracheostomy, the animals were ventilated with room air from a respirator, using 20 ml/kg at 18–24 rpm, and Pa_{O_2} and Pa_{CO_2} were kept at 90–105 and 35–45 mmHg, respectively. A femoral vein was catheterized for administration of medications and maintenance saline. Rectal temperature was continuously monitored, and it was maintained at 37 ± 1° C by the use of a heating blanket.

To monitor the systemic blood pressure (SBP) and for periodic sampling of blood gases, a catheter was placed in the abdominal aorta *via* the femoral artery. The mean SBP was calculated as the diastolic pressure plus one-third of the pulse pressure.

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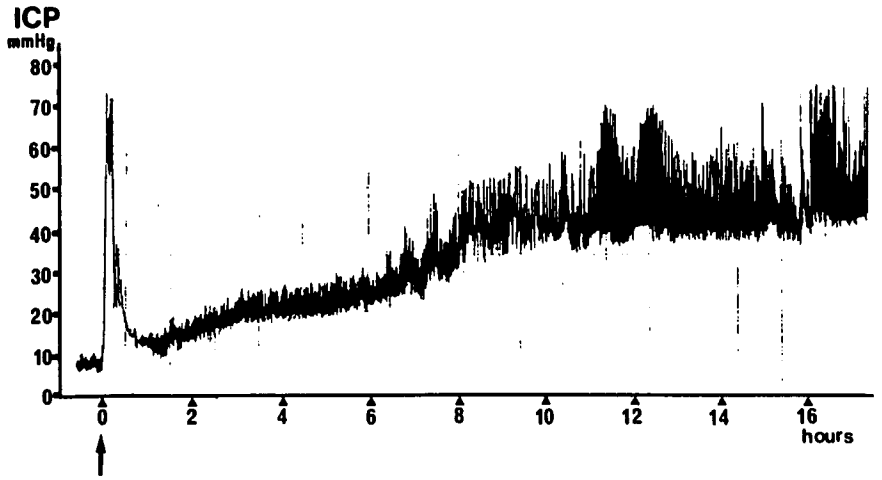

FIG. 1. An example of intracranial hypertension that followed intracisternal injection of 10 ml of incubated blood. ICP = intracranial pressure. Solid arrow indicates the time when incubated blood was injected. Paper-chart speed = 2 cm/hr.

PLACEMENT OF CANNULAE AND ICP MONITORING

With the animal prone and the head elevated and fixed in the stereotaxic frame, the calvaria was exposed. Using a high-speed drill, burr holes were made for placement of cannulae for the ICP monitoring and the application of pentobarbital into the subcortical brain sites.

The ICP was recorded through a 16-gauge needle inserted stereotaxically into the lateral ventricle and connected to a pressure transducer. A horizontal plane through the orbitomeatal line was used as zero reference level for the ICP monitoring. The mean ICP was calculated as the diastolic pressure plus one-third of the pulse pressure. The cerebral perfusion pressure (CPP) was determined as the difference between the mean SBP and the mean ICP.

Placement of cannulae into the desired subcortical brain sites, *i.e.*, the posterior hypothalamus, pontine reticular formation, or medullary reticular formation, was achieved under stereotaxic guidance according to Lim *et al.*[15] The location of the cannulae corresponded anatomically to the areas from the posterior hypothalamus to the nucleus hypothalamicus dorsomedialis, the pons to the nucleus reticularis pontis oralis, and the medulla to the nucleus reticularis parvicellularis, respectively. The location of the medullary cannula corresponded to the region of the vasomotor center.[16]

The burr holes for the placement of the cannulae for ICP monitoring and drug application were sealed with dental acrylic and adhesive, and care was taken not to let the cerebrospinal fluid (CSF) leak from the holes.

ELECTROENCEPHALOGRAPHIC RECORDINGS

Cortical activity was recorded from bilateral epidural screw bolts located over the frontal region (the posterior sigmoid gyrus). Bipolar electrodes, which were made from Teflon-coated stainless steel tubing with an outer diameter of 500 μ inserted into two Teflon-coated tungsten filaments with a diameter of 125 μ each, were inserted stereotaxically[15] into the following regions: dorsal hippocampus and intralaminal nuclei of the thalamus.

SUBARACHNOID BLOOD INJECTION

Blood was injected through an 18-gauge needle into the chiasmatic cistern. The method used was according to McQueen and Jeans,[17] *i.e.*, the needle was introduced under the zygomatic arch at a point 2 cm below the external canthus and directed to the optic foramen at an angle of 45° with the sagittal plane. The tip was inserted through the foramen and encountered resistance. Ten ml of autogenous whole blood incubated at a temperature of 37° C in a test tube in an incubator for 3 days was prepared for the injection into the chiasmatic cistern. Clinical and experimental studies have suggested that blood in the subarachnoid space produces a meningeal inflammatory reaction, hydrocephalus, and/or vasospasm with acute ischemic edema, and the reactions caused by incubated blood are more severe and intense than those resulting from fresh blood.[18–22]

Injections were done by hand; infusions were made at the pressure of 50–70 mmHg through the needle placed in the chiasmatic cistern. The infusion time was 5–15 min.

Figure 1 shows a typical example of the intracranial hypertension that followed the 10-ml intracisternal blood injection. The ICP rose to about 65 mmHg during the blood infusion, subsequently falling to the original level within a few minutes. Thereafter, the ICP slowly increased with frequent ICP irregularities. Using this experimental model, the following studies were carried out.

PROTOCOL

The study protocol is shown in table 1. The animals were randomly divided into four groups: group I consisted

TABLE 1. Study Protocol and Number of Animals Examined

Material Administered	Dose	Brain Sites Administered		
		Hypothalamus (Group I)	Pons (Group II)	Medulla (Group III)
d-Glucose	2 mg	5 (3)	5 (3)	5 (3)
Pentobarbital sodium	0.4 mg	5 (2)	5 (2)	6 (2)
Pentobarbital sodium	2 mg	6 (3)	6 (5)	6 (4)
[Group IV]				
Evans blue	0.4 mg	2	2	2
Evans blue	2 mg	2	2	2

Numbers in parentheses indicate the number of dogs in whom electroencephalographic studies were carried out.

of 16 animals given pentobarbital or d-glucose into the hypothalamus; group II—16 animals in whom the drugs were administered into the pons; and group III—17 animals in whom the drugs were administered into the medulla. Group IV consisted of 12 animals receiving dye into the subcortical brain sites.

Application of Pentobarbital or d-Glucose

A solid form of pentobarbital sodium in the experimental animals or d-glucose in the control animals was applied into the desired subcortical brain sites by implanting the chemical compounds into the brain. The technique for applying small quantities of chemicals was based on that described by Yamaguchi *et al.*[23] Twenty-gauge stainless steel hypodermic tubing was placed into the desired brain sites. The inside stylet of the cannula was removed. Another polyethylene tubing, into the tip of which the desired amount of chemicals had been packed, was fitted snugly over the exposed end of the cannula by a special holder made from a 17-gauge hypodermic needle. The chemicals were then introduced into the cannula and the original stylet returned to its usual position in the cannula. Thus, the chemicals to be studied were inserted directly into the brain site.

Both pentobarbital and d-glucose were administered when the ICP rose to between 20 and 30 mmHg after the blood injection, usually within 3–6 h. Pentobarbital or d-glucose was introduced bilaterally and simultaneously. Usually, 1 or 0.2 mg of pentobarbital or 1 mg of d-glucose was introduced per cannula in each animal, and, hence, total dose of pentobarbital or d-glucose was 2 mg or 0.4 mg in each animal (table 1).

Dye Dispersion

To estimate the dispersion of locally administered drugs, 2 mg and 0.4 mg of Evans blue was introduced into the posterior hypothalamus, pons, or medulla in the same way as the application of pentobarbital or d-glucose using the 12 experimental model animals (table 1).

Autopsy

The animals administered pentobarbital, d-glucose, or dye were killed with an intravenous injection of thiopental followed by KCl at 12 h after the introduction of materials. Autopsies were performed on all dogs for confirmation of the cannulae and electrodes inserted into the brain sites or distribution of dye.

Analysis

The results are expressed as mean ± SEM. The mean values and SEM of the mean ICP, mean SBP, and CPP in each group were calculated at 0, 2, 4, 6, 8, and 10 h after pentobarbital or d-glucose introduction. Analysis of variance was used for inter- and intragroup comparisons. The differences then were subjected to the modified *t* test according to the method of Bonferroni.[24] A value of $P < 0.05$ was considered significant.

Results

Mean ICP Changes

The time course of the mean ICP after pentobarbital application in the experimental animals and d-glucose in the control animals in all three groups are shown in figure 2. The animals administered both the 2-mg and 0.4-mg doses of pentobarbital in the medulla showed a significant decrease ($P < 0.01$) of the mean ICP compared with the animals administered d-glucose, whereas those receiving pentobarbital at the other sites did not. The mean ICP decreased significantly ($P < 0.01$) for at least 4 h following the 0.4-mg dose of pentobarbital and a significant reduction ($P < 0.01$) of the mean ICP persisted for 6 h after the 2-mg dose of pentobarbital. The greatest ICP reduction of the 0.4-mg dose of pentobarbital was seen at 2 h, at which time the mean ICP was 65% of control. The greatest effect of the 2-mg dose of pentobarbital was also demonstrable at 2 h, at which time the mean ICP was 44% of control (fig. 2). Figure 3 shows examples of the ICP response before and after the administration of 2 mg of d-glucose, 2 mg and 0.4 mg of pentobarbital at the medulla, respectively. The increasing ICP showed a marked drop after the pentobarbital application into the medulla (fig. 3B,C), whereas it showed no decrease after the d-glucose application (fig. 3A).

Mean SBP and CPP Changes

Simultaneous recordings of the ICP, SBP, and CPP were carried out in all animals throughout the study. Changes of the mean SBP and CPP in each group are shown in figure 4. In group I and II animals administered the 2-mg and 0.4-mg doses of pentobarbital, the mean

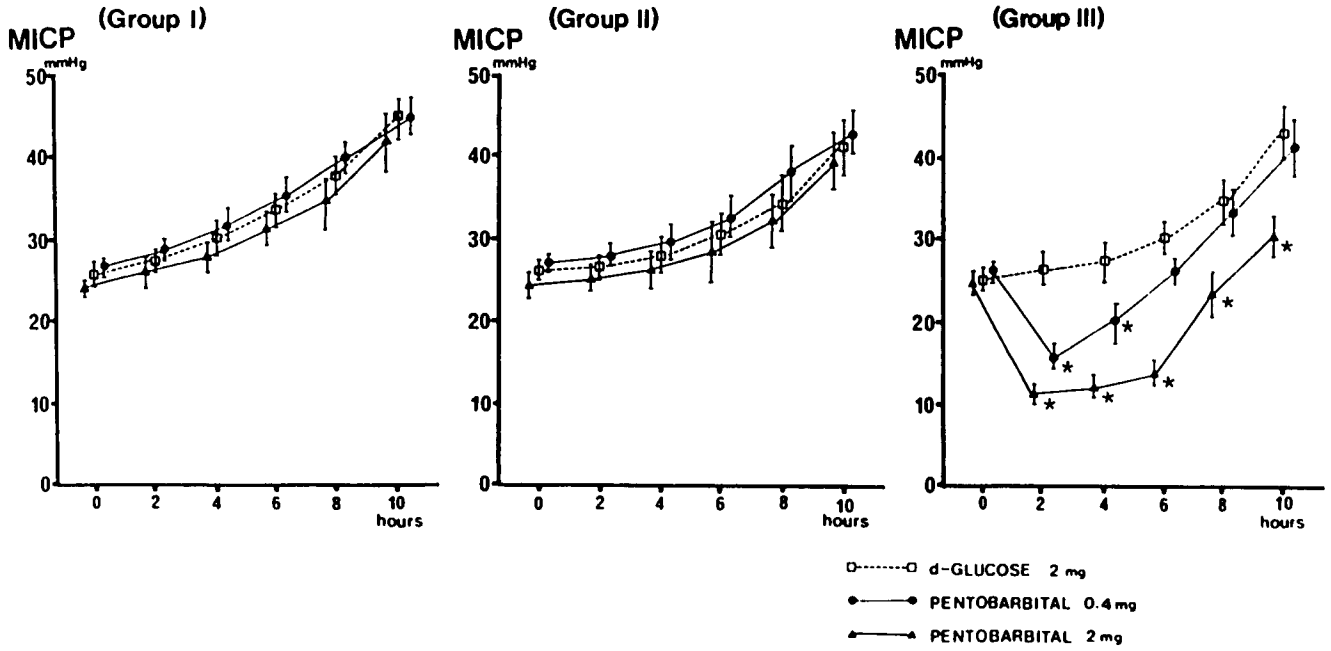

FIG. 2. Sequential changes in mean intracranial pressure (MICP) in animals with the application of pentobarbital or d-glucose in each group. Standard error of mean is shown by the vertical bars. *$P < 0.01$ indicates significant difference compared to controls at the same time period after the drug introduction.

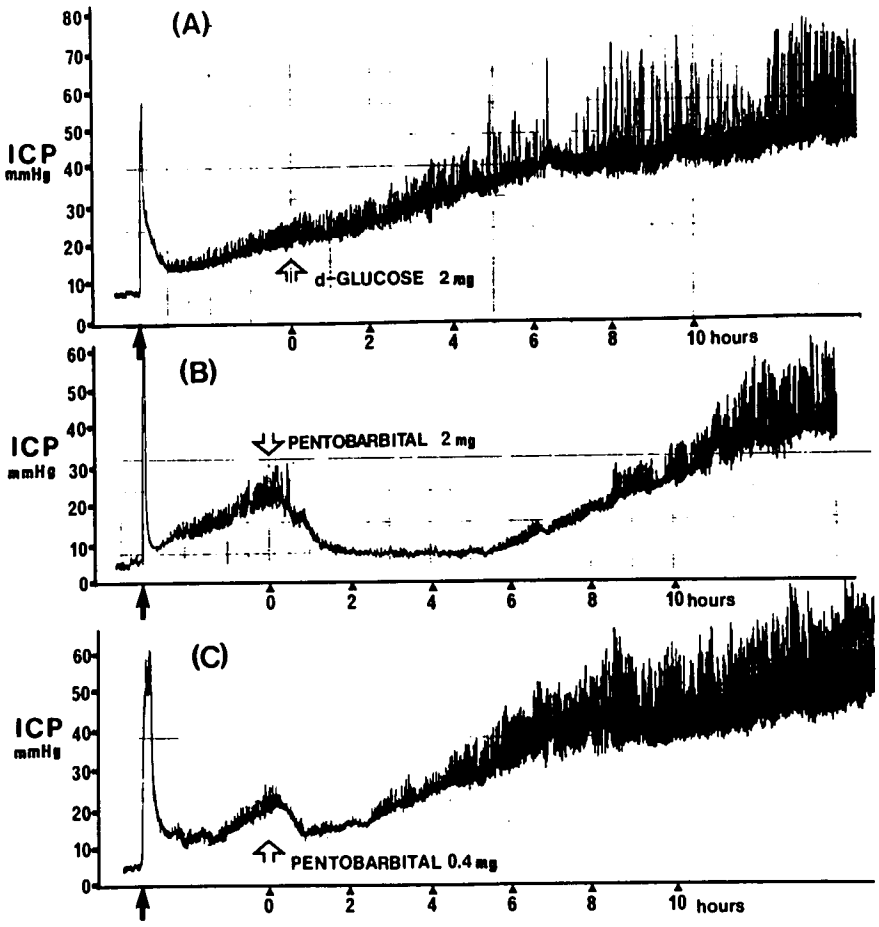

FIG. 3. Examples of intracranial pressure (ICP) before and after the administration of 2 mg of d-glucose (*A*), 2 mg (*B*) or 0.4 mg (*C*) of pentobarbital into the medulla oblongata. Solid arrows indicate the time when incubated blood was injected, and open arrows denote the time when drugs were introduced. Paper-chart speed = 2 cm/hr.

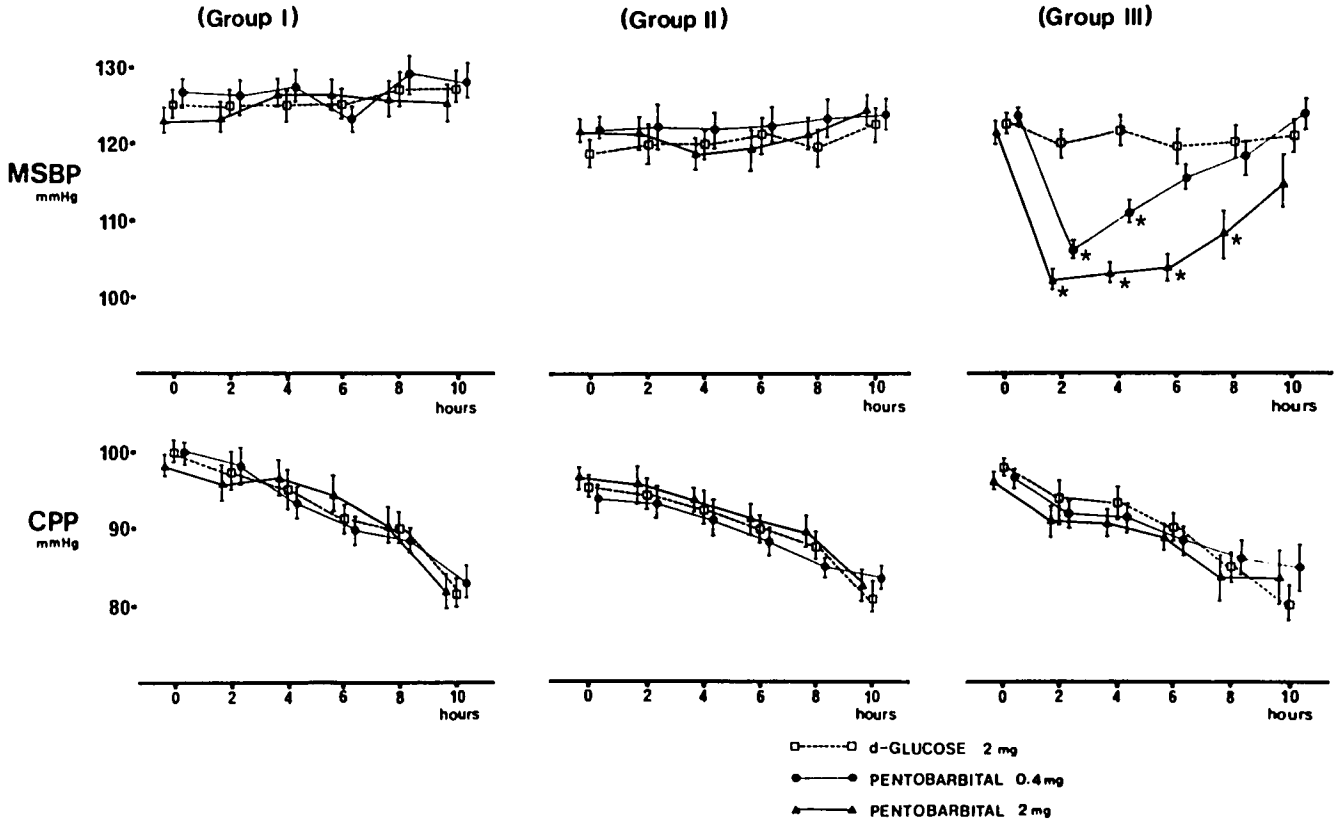

FIG. 4. Sequential changes in mean systemic blood pressure (MSBP) and cerebral perfusion pressure (CPP) in animals with the application of pentobarbital and d-glucose in each group. Standard error of mean is shown by the vertical bars. *$P < 0.01$ denotes significant difference from controls at the same time period after drug injection.

SBP showed no significant changes compared with the animals administered d-glucose. In group III animals administered the 2-mg and 0.4-mg doses of pentobarbital, the mean SBP decreased significantly ($P < 0.01$) compared to the SBP change in the animals given d-glucose. The decrease in mean SBP of the 0.4-mg dose of pentobarbital was seen for 2 h after injection, at which time the mean SBP was 88% of control. The effect of the 2-mg dose of pentobarbital was also demonstrable at 2 h, at which time the mean SBP was 80% of control.

Sequential changes in the CPP were nearly identical for groups I, II, and III, whether given d-glucose or pentobarbital (fig. 4).

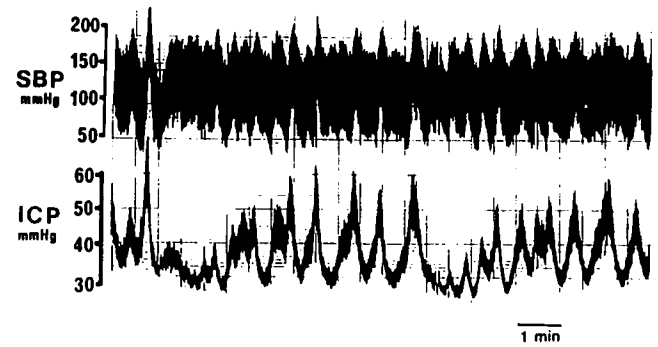

FIG. 5. An example of the simultaneous recording of the systemic blood pressure (SBP) and intracranial pressure (ICP), showing marked concomitant fluctuations in both the SBP and ICP. Paper-chart speed = 2 cm/min.

ICP Irregularities and SBP Variations

In all animals in groups I and II and in the d-glucose administered animals in group III, the increasing ICP was always accompanied by ICP irregularities, and the higher the ICP baseline, the more frequent and greater the ICP irregularities (figs. 3A, 5). On the other hand, the animals administered the 2-mg and 0.4-mg doses of the pentobarbital into the medulla showed a reduction of these ICP irregularities when a decrease of the ICP baseline was obtained (figs. 3B,C). The ICP curve in these animals, however, showed irregularities when the ICP again increased.

The ICP irregularities observed were always accompanied by marked fluctuations in the SBP. These SBP fluctuations became more marked and greater when the ICP irregularities rose in amplitude and were only suppressed in group III animals with the pentobarbital administration. Figure 5 is an example of the simultaneous

recording of the SBP and ICP, showing marked fluctuations in the ICP accompanied by SBP variations obtained in one dog administered d-glucose into the hypothalamus.

Electroencephalographic Findings

The electroencephalograms (EEG) were recorded in 27 animals (table 1). EEG desynchronizations in both the cortical and subcortical activities in the 15–25 Hz range were usually noticed in animals showing the increased ICP and ICP irregularities after the intracisternal blood injection. A typical EEG pattern is shown in figure 6A. The animals treated with both the 2-mg and 0.4-mg doses of pentobarbital into the medulla had a marked change in the EEG when the ICP decreased, whereas those in whom pentobarbital was introduced at the other sites or those given d-glucose did not. The change was characterized by the appearance of high amplitude, random slow waves in the 3–8 Hz range. Figure 6B shows an example of the EEG change after 2 mg pentobarbital was injected into the medulla. There were no epileptic dischages before and after the administration of drugs into the subcortical brain sites.

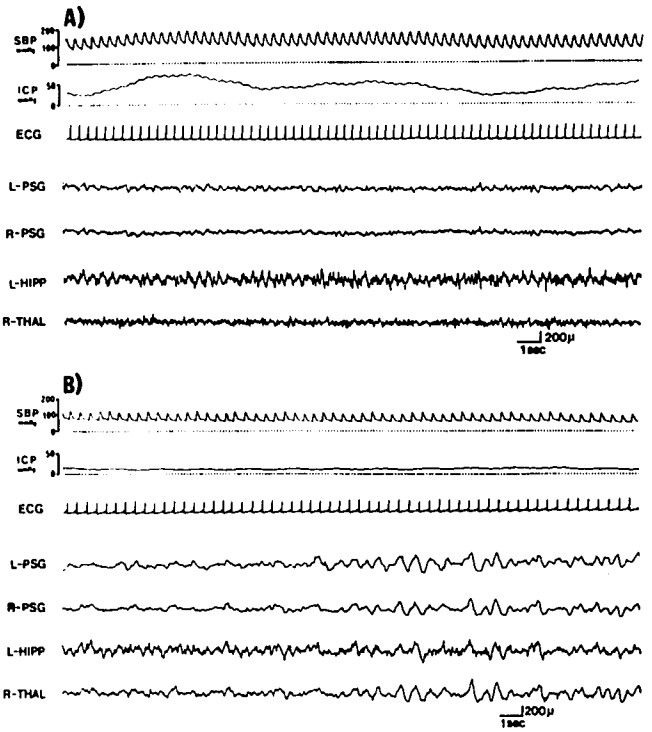

FIG. 6. Electroencephalographic recordings. *A.* Typical pattern showing desynchronizations in the cortical and subcortical activities obtained in one animal with high intracranial pressure (ICP) and ICP irregularities. *B.* Typical pattern showing high voltage random slow waves obtained in one animal with low and flat ICP pattern after 2 mg of pentobarbital into the medulla. SBP = systemic blood pressure; ECG = electrocardiogram; PSG = posterior sigmoid gyrus; HIPP = hippocampus; THAL = thalamus; L = left; R = right.

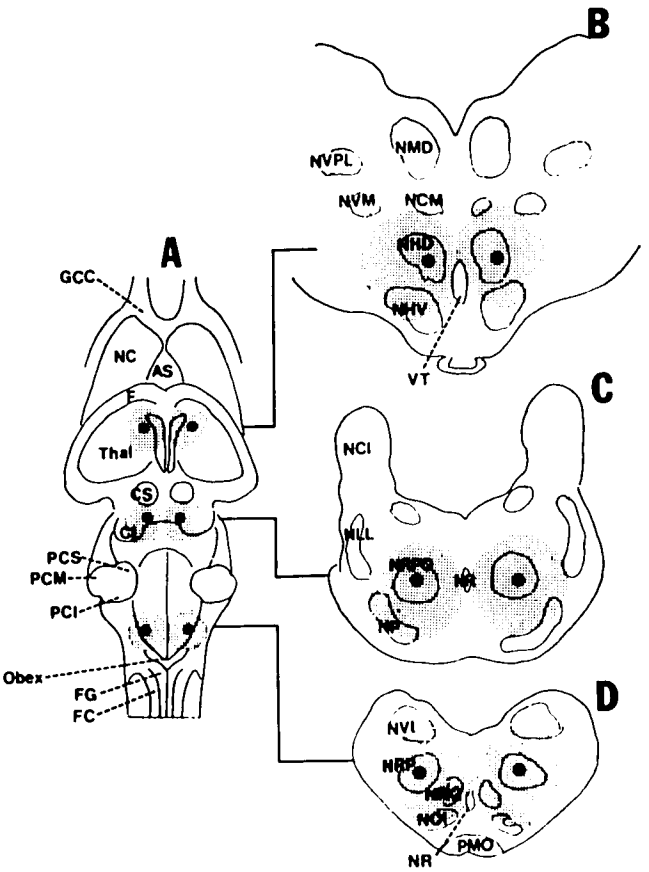

FIG. 7. Schema showing dye dispersion based on six animals injected with the 2-mg dose of dye into each subcortical brain site. Solid circles indicate the points that the tips of cannulae were placed. Shaded areas denote the distribution of dye. *A.* Dorsal surface of the brain stem and subcortex after removal of overlying cerebellum and cerebral cortex. *B–D.* Cross sections through the medulla, pons, and hypothalamus at levels indicated by guidelines to A. AS = area septalis; CI = colliculus inferior; CS = colliculus superior; F = fornix; FC = fasciculus cuneatus; FG = fasciculus gracilis; GCC = genu corporis callosi; NC = nucleus caudatus; NCI = nucleus colliculi inferior; NCM = nucleus centralis medialis; NHD = nucleus hypothalamicus dorsomedialis; NHV = nucleus hypothalamicus ventromedialis; NLL = nucleus lemnisci lateralis; NMD = nucleus medialis dorsalis; NOI = nucleus olivaris inferior; NP = nuclei pontis; NR = nucleus raphes; NRG = nucleus reticularis gigantocellularis; NRP = nucleus reticularis parvicellularis; NRPO = nucleus reticularis pontis oralis; NVI = nucleus vestibularis inferior; NVM = nucleus ventralis medialis; NVPL = nucleus ventralis posterolateralis; PCI = pedunculus cerebelli inferior; PCM = pedunculus cerebelli medius; PCS = pedunculus cerebelli superior; PMO = pyramis medullae oblongatae; Thal = thalamus; VT = ventriculus tertius.

Dye Distribution

The distribution of dye appeared to be well localized. The dye spread globularly to the neighboring structures, with a diameter of 7–8 mm by 2 mg dye, and 4–5 mm by 0.4 mg dye. Figure 7 shows the schema illustrating the dye dispersion based on six animals injected with the 2-mg dose of dye into each subcortical structure.

Discussion

Jackson[20] has reported that autogenous fresh blood causes a slight meningeal reaction, whereas whole blood incubated for 3 days or longer elicits severe aseptic meningitis in dogs. Bagley[18] also observed that intermittent intracisternal injection of whole blood causes aseptic meningitis in dogs. It has been suggested that incubated blood and breakdown products of erythrocytes might produce prolonged cerebral vasospasm and hydrocephalus.[21,22,25,26] In the present study, intracranial hypertension following SAH was induced by the injection of incubated blood. From the results previously reported, the cause of the elevated ICP after intracisternal blood injection might be a meningeal inflammatory reaction, hydrocephalus, and/or cerebral vasospasm with ischemic edema.

Chorobski and Penfield[27] found that there was a pathway for efferent impulses from the medulla to the cerebral vessels, and that electrical stimulation at any point on this pathway produces dilatation of the arterioles of the pia mater. Forbes and Cobb[28] also showed that stimulation of the facial nerve at the geniculate ganglion caused prompt dilatation of the arteries in the pia mater of the parietal region. Langfitt and Kassell[29] revealed that stimulation of various parts of the brain stem and hypothalamus caused a dilatation of the cerebral vessels resulting in a rise in the ICP, and suggested that this could have been due to activation of the Chorobski-Penfield pathways. There are abundant nerve supplies to the cerebral arteries,[30] and it has recently been shown that some of these fibers are derived from the brain stem.[31-34] These reports suggest that the tone and reactivity of the cerebral arteries may change in accordance with the intrinsic activity of the brain stem.

All barbiturates possess a low degree of specificity of action, and hence produce a similar pattern of depression of the central nervous system. Neurophysiological studies in animals and humans suggest that the depression of the central nervous system results from suppression of the reticular activating system.[10,12] In the present study, we administered pentobarbital locally in the posterior hypothalamus, pontine reticular formation, or medullary reticular formation, so as to prevent the drug from reaching diverse parts of the brain where its effects may be complex. It has been claimed that chemical agents can be more precisely localized by depositing them in solid, rather than liquid, form.[35,36] In this study, the drugs were given in the solid form. The distribution of the drugs administered into the subcortical brain sites was estimated by the use of dye. The dye spread spherically to the neighboring structures, and its distribution remained localized and restricted.

It is still not clear whether the effect of reducing elevated ICP requires anesthetic doses. In the clinical setting, however, high-dose barbiturate anesthesia is often utilized.[37] In this study, we applied both a relatively high dose (2 mg) and a relatively low dose (0.4 mg) of pentobarbital locally, and they showed similar effects on increased ICP, as well as the SBP and CPP, aside from the continuation of their effects.

It has been suggested that barbiturates are cardiovascular depressants, and, hence, it might be expected that the reduction in ICP is a reflection of the fall in the SBP.[38] In the present study, the animals in whom pentobarbital was introduced into the medulla had a significant decrease in both the ICP and SBP. Our results, therefore, suggest that the application of pentobarbital was introduced into the medulla could result in a primary systemic vasodepressor response, leading to a secondary reduction in the ICP.

Several factors may influence the EEG after SAH. They include raised ICP, vasospasm, hydrocephalus, and blood itself in the subarachnoid space. Ketamine anesthesia used in this experiment also has effects on the EEG. On the other hand, one characteristic in the present study was the occurrence of ICP irregularities associated with the SBP variations. It has been believed that the ICP irregularities are related to an intrinsic activity of the medullary centers, released from the influence of higher centers in the upper brain stem, and regarded as a sign of brain stem dysfunction or instability of the vasomotor center.[14,39] It has also been reported that the EEG desynchronizations occurred in patients with acute brain stem damage,[40,41] and this finding was also observed in experimental study.[42] In the present study, the EEG showed desynchronized patterns in animals with increased ICP and ICP irregularities, and the EEG patterns were replaced by the high voltage slow waves in animals with low and flat ICP patterns after pentobarbital injection into the medulla. These observations suggest that the EEG desynchronizations associated with the ICP irregularities may indicate a sign of instability or dysfunction of the brain stem, and the EEG slow wave patterns may indicate a reduced state of this instability.

In the present study, the animals injected with pentobarbital into the medulla demonstrated both a significant decrease in the ICP and a stabilization of ICP irregularities. The SBP was also depressed and the SBP variations were stabilized in animals with the pentobarbital administration into the medulla. Our results suggest that, in the presence of elevated ICP caused by SAH, barbiturates may, by depressing the medullary vasomotor center, cause a reduction in ICP caused by cerebral vascular excitatory responses.

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