Neuronal damage in rat brain and spinal cord after cardiac arrest and massive hemorrhagic shock*

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Objectives: Severe global ischemia often results in severe damage to the central nervous system of survivors. Hind-limb paralysis is a common deficit caused by global ischemia. Until recently, most studies of global ischemia of the central nervous system have examined either the brain or spinal cord, but not both. Spinal cord damage specifically after global ischemia has not been studied in detail. Because the exact nature of the neuronal damage to the spinal cord and the differences in neuronal damage between the brain and spinal cord after global ischemia is poorly understood, we developed a new global ischemia model in the rat and specifically studied spinal cord damage after global ischemia. Further, we compared the different forms of neuronal damage between the brain and spinal cord after global ischemia.

Design: Randomized, controlled study using three different global ischemia models in the rat.

Setting: University research laboratory.

Subjects: Male, adult Sprague-Dawley rats (300 g).

Interventions: Animals were divided into three experimental groups. Group A (n = 6, survived for 7 days), 12 mins of hemorrhagic shock; group B (n = 6, survived for 7 days), 5 mins of cardiac arrest; or group C (n = 6, each for 6 hrs, 12 hrs, 1 day, 3 days, and 7 days), 7 mins of hemorrhagic shock and 5 mins of cardiac arrest. Motor deficit of the hind limbs was studied 6 hrs to 7 days after resuscitation. Also, nonoperated animals (n = 6) were used as the control. Histologic analysis (hematoxylin and eosin, Fluoro-Jade B, terminal deoxynucleotidyl transferase-mediated dUTP end-labeling [TUNEL], Klüver-Barrera) and ultrastructural analysis using electron microscopy were performed on samples from the CA1 region of the hippocampus and lumbar spinal cord. Demyelination of the white matter of the lumbar spinal cord was analyzed semiquantitatively using Scion Image software.

Main Results: No paraplegic animals were observed in either group A or B. All group C animals showed severe hind-limb paralysis. Severe neuronal damage was found in the CA1 region of the hippocampus in all groups, and the state of delayed neuronal cell death was similar among the three groups. Neuronal damage in the lumbar spinal cord was detected only in group C animals, mainly in the dorsal horn and intermediate gray matter. Demyelination was prominent in the ventral and ventrolateral white matter in group C. A significant difference was observed between control and group C rats with Scion Image software. Ultrastructural analysis revealed extensive necrotic cell death in the intermediate gray matter in the lumbar spinal cord in group C rats.

Conclusion: The combination in the global ischemia model (i.e., hemorrhagic shock followed by cardiac arrest) caused severe neuronal damage in the central nervous system. Thereby, hind-limb paralysis after global ischemia might result from spinal cord damage. These results suggest that therapeutic strategies for preventing spinal cord injury are necessary when treating patients with severe global ischemia. (Crit Care Med 2006; 34:2820–2826)

Keywords: global ischemia; cardiac arrest; spinal cord injury; paraplegia; demyelination; necrotic neuronal cell death

See also p. 2865.

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S evere global ischemia, such as prolonged hypotension and cardiac arrest, is a major cause of serious damage to the central nervous system. In recent years, advances in medical technology have increased the number of patients who survive cardiac arrest/cardiopulmonary resuscitation (CPR) (1–3). However most of the survivors have both physiologic and behavioral deficits (4, 5). Hind-limb paralysis is one of the major deficits after global ischemia. Several clinical case reports have presented hind-limb paralysis after cardiac arrest (6, 7), and one retrospective study has demonstrated the vulnerability of the lumbosacral spinal cord to damage after cardiac arrest and hypotension (8).

Ischemic damage of the brain and spinal cord has been investigated separately in many studies, and brain damage after global ischemia, especially, has been investigated extensively (9–11). However, few studies have shown spinal cord damage after global ischemia, although many clinical (12) and clinicopathologic studies (13, 14) have indicated that global ischemia affects the lumbar spinal cord. Moreover, few studies have simultaneously examined brain and spinal cord damage after global ischemia. Therefore, the spinal cord damage and the differences in neuronal damage between the brain and spinal cord after global ischemia are poorly understood.
We hypothesized that a) hind-limb paralysis after global ischemia is caused by spinal cord damage and that b) the brain and spinal cord have different vulnerabilities to a global ischemic event. Here, we have examined the neuronal damage in the brain and spinal cord after global ischemia with three different ischemia models.

**MATERIALS AND METHODS**

**Animals.** Adult, male Sprague-Dawley rats weighing between 250 and 300 g were used in the study. They were allowed free access to food and water and maintained on a 12-hr light/dark cycle at 23°C with constant humidity (40% ± 15%). All experimental procedures involving animals were approved by the Institutional Animal Care and Use Committee of Showa University, Tokyo, Japan (approval 04112).

**Surgical Preparation.** Rats were intubated and anesthetized with inhalation of 2.0% sevoflurane and 70% N₂O in oxygen. Rectal temperature was maintained at 37.0°C with a heat blanket. The left femoral artery and tail artery were dissected free and were inserted with a polyethylene catheter (PE-50) for withdrawal of arterial blood and for monitoring of mean arterial blood pressure (MAPB), respectively. During surgery, cardiac monitoring was performed using an electrocardiograph with subcutaneous needle electrodes. After these procedures, heparin (100 units/kg) was administered intra-arterially to avoid blood clot formation. Arterial blood samples were analyzed before ischemia and 10 mins after resuscitation.

**Experimental Protocol of Hemorrhagic Shock and Cardiac Arrest.** Rats were divided into three groups: group A (n = 6, followed up for 7 days only) animals were administered 12 mins of hemorrhagic shock. Hemorrhagic shock was induced by withdrawing 3 mL/100 g arterial blood (15, 16). Resuscitation from hemorrhagic shock was performed by re-infusing the shed blood. Group B (n = 6, for 7 days only) rats were administered 5 mins of cardiac arrest, according to the modified chest compression-induced cardiac arrest method described previously (17, 18). In brief, the operator gently compressed the rat’s chest with two fingers (index and middle) with similar force as generated by a 3 kg weight, thereby inducing the cessation of ventilation. Cardiac arrest was confirmed by the diminutions of MAPB and heart rate. The end point of compression was the complete loss of pulse pressure. Artificial ventilation and anesthesia were stopped during cardiac arrest. After 5 mins of cardiac arrest, CPR was performed by artificial ventilation with 100% oxygen and manual cardiac massage. Group C rats (n = 6 each, for 6 hrs, 12 hrs, 1 day, 3 days, 7 days) received 7 mins of hemorrhagic shock and 5 mins of cardiac arrest. First, hemorrhagic shock was induced by the same method as described for group A. After 7 mins, cardiac arrest was also induced by chest compression, as described above for group B. After 5 mins of cardiac arrest, CPR was performed with 100% oxygen ventilation, re-infusion of shed blood, and manual cardiac massage. As soon as restoration of spontaneous circulation was achieved, defined as a sustained systolic MABP of 60 mm Hg, cardiac massage was stopped. If restoration of spontaneous circulation could not be achieved within 3 mins of CPR, the animal was not used further. Ten minutes after restoration of spontaneous circulation and ventilation, animals were weaned from the ventilator and returned to their cages. Serial assessments of their hind-limb motor functions was performed by an investigator (who was unaware of the group of each animal) at 1 hr, 6 hrs, 12 hrs, 1 day, 3 days, and 7 days after resuscitation. To prevent dehydration, lactated Ringer solution (2 mL/100 g, subcutaneously) was given and repeated daily until the rats started to drink spontaneously. Normal control rats (n = 6) received no surgical procedures except for spinal cord removal under deep anesthesia.

**Evaluation of Neurobehavioral Outcomes.** To evaluate the neuronal damage, motor function deficits in the hind limbs were evaluated according to criteria previously proposed (19). Motor deficit scores were graded according to the following scale: a) walking/use of hind limbs: 0 scored as normal, 1 for toes flat under the body when walking, 2 for knuckle walking, 3 for movement of the hind limbs but unable to walk; and 4 for no movement, dragging hind limbs; b) placing/stepping reflex: 0 scored for normal, 1 for weak, and 2 for not stepping. Each motor deficit score was obtained by adding the scores for scales a and b. Animals with motor deficit scores of ≥4 were considered paraplegic.

**Tissue Preparation.** After resuscitation, the animals were anesthetized with pentobarbital (50 mg/kg, intravenously) and transcardially perfused with 0.9% NaCl, followed by 4% paraformaldehyde in 50 mM phosphate buffer (pH 7.2). The brain and spinal cord were removed (i.e., control, 1 day, and 7 days with 0.4% glutaraldehyde in 0.1 M phosphate buffer (pH 7.2). The next day, the lumbar spinal cord was dissected free and were inserted with a vibratome into 40-µm-thick sections. The intermediate gray matter and ventral white matter of the lumbar spinal cord were further processed by postfixation in 1% osmium tetroxide in 0.1 M phosphate buffer for 1 hr at 4°C. The samples were then dehydrated through a graded ethanol series and embedded in Epon-Araldite. Polymerization was performed at 65°C for 72 hrs. The blocks were then cut on an ultramicrotome, collecting ultrathin sections 60–70 nm thick. The ultrathin sections were poststained with 1% uranyl acetate in ethan, followed by 0.1% lead citrate dissolved in 0.1 M sodium hydroxide. Finally, these sections were observed with a Hitachi H-7000 electron microscope.

**Semiquantification of Spinal Cord White Matter Demyelination.** Demyelination of the lumbar spinal cord was examined with Klüver-Barrera staining. The images were obtained from left and right hemisected in ventral white matter, and corticospinal tract. Three regions of the white matter were evaluated by taking images with an objective lens (×40). The size of the photo-image was 289.3 × 228.6 µm. The stained area was subjected to semiquantification analysis of demyelination using the Scion Image program that was developed at the National Institutes of Health (23, 24) and was calculated as the percentage of the total area of the image. These procedures were performed by an investigator who was unaware of the group of each animal.

**Statistical Analysis.** Data are expressed as mean ± SEM. One-way analysis of variance was performed and followed by Bonferroni post hoc test. Values of p < .05 were considered statistically significant.

**RESULTS**

**Physiologic Variables.** Arterial blood gas readings were shown in Table 1. Before ischemia, variables in all groups were within the normal range. Ten minutes after resuscitation, massive acidosis and hyperglycemia were found in all groups, and particularly in group C animals. Significant differences between group C and the other two groups were...
observed in Pco2, base excess, and glucose levels.

Before ischemia, MABP was 100 ± 10 mm Hg and heart rate was 420 ± 20 beats/min. In group A rats, MABP decreased (<20 mm Hg) markedly after the withdrawal of arterial blood, yet no significant change was seen in heart rate. In group B animals, MABP decreased to <10 mm Hg soon after chest compression, and heart rate decreased to approximately 30% of baseline. The changes to MABP, heart rate, and electrocardiogram waveforms in group C rats are shown in Figure 1, A–C. The induction of cardiac arrest after hemorrhagic shock caused a second decrease in MABP of <10 mm Hg, and the electrocardiogram showed pulseless electrical activity or asystole. Within 2 mins of commencing CPR, all surviving rats recovered spontaneous circulation, and 80% recovery of MABP was achieved within 5 mins after CPR in most animals (26 of 30 rats).

Neurobehavioral Outcomes. The time course of motor deficit scores in the three groups is presented in Figure 1D. The animals in groups A and B showed return of almost-normal motor function of their hind limbs within 6 hrs of resuscitation. No paraplegia was observed in either group A or B rats during the experimental period. In contrast, the animals in group C showed severe motor deficits, including flaccid and spastic paraplegia. Six hours after resuscitation, most of these animals were still unconscious, although breathing spontaneously, but no movement was observed. These rats had regained consciousness and some moved their hind limbs slightly 1 day after resuscitation. However, they could not stand or walk, and most of them exhibited spastic paralysis, except for a few rats (5 of 30 rats) that still showed flaccid paralysis. Therefore, most of the animals required subcutaneous injection of lactated Ringer solution to maintain hydration. By day 3, the animals could walk again with their fore limbs and had recovered normal feeding behavior. All animals showed spastic paralysis in their hind limbs, which persisted throughout the experiment.

Histologic Examination of the CA1 Region of the Hippocampus. Sections from control and group C rats are presented in Figure 2. With hematoxylin and eosin staining (Fig. 2, a–d), the CA1 region of the hippocampus in control animals exhibited normal neuronal structure (i.e., large, round, individual nuclei with a distinct nucleus and pyramidal arrangement of three to five layers) (Fig 2a). On day 1 in group C rats, the shape of neuronal nuclei was slightly abnormally eosinophilic but was not changed in structure (Fig. 2b). On day 3 in group C rats, eosinophilic staining was more prominent in the cytoplasm, and shrunken cell bodies were observed (Fig. 2c). Severe neuronal shrinkage and loss were observed in the hippocampal CA1 region on day 7 in group C rats, and the typical pyramidal layered structure had completely collapsed (Fig. 2d).

There was no FJB staining of neurons in the CA1 region of the hippocampus in the control animals (Fig. 2e). However, the intensity of FJB-positive staining around nuclei in neurons progressively increased 1–3 days after resuscitation in group C rats (Fig. 2, f and g). On day 7, FJB-positive staining was extensively noted in neurons in the CA1 region of the hippocampus, associated with marked shrinkage of these neurons (Fig. 2h).

TUNEL staining of sections from control and group C rats are shown in Figure 2, i–l. No positive neuron was seen in control animals. Few positive neurons were detected on day 1. TUNEL-positive neurons were clearly detected 3 days after resuscitation, and almost all neurons (>90%) in the CA1 region were TUNEL positive on day 7. In group A and B rats, similar changes were observed on day 7 in each staining (data not shown). The

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Table 1. Physiologic variables in the three groups of animals

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<td>Pco2, mm Hg</td>
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<td>84.4 ± 7.2*</td>
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<td>Po2, mm Hg</td>
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<td>120.2 ± 9.4</td>
<td>90.7 ± 6.9</td>
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<td>BE, mmol/L</td>
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<td>1.4 ± 0.3</td>
<td>-6.0 ± 0.9</td>
<td>-7.1 ± 1.7</td>
<td>-10.7 ± 1.1*</td>
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<td>Glucose, mg/dL</td>
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<td>134.2 ± 8.9</td>
<td>136.9 ± 8.5</td>
<td>191.8 ± 10.3</td>
<td>197.0 ± 11.7</td>
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<td>Ht, %</td>
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<td>36.1 ± 1.0</td>
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*p < .05. Data provided as mean ± SEM.
features of cell death in the hippocampus after resuscitation in all three treatment groups were similar to those of delayed neuronal cell death, as previously reported (25–27).

**Histologic Examination in the Gray Matter of the Lumbar Spinal Cord.** In sections collected from group A and B rats, there were no obvious morphologic changes to neurons, and no FJB-positive and TUNEL-positive cells were detected up to 7 days after resuscitation (data not shown).

In group C rats, the time course of neuronal cell death in the gray matter of the lumbar spinal cord was quite different to that seen in the hippocampus. With hematoxylin and eosin staining (Fig. 3, a–d), some neurons 6 hrs after resuscitation showed mild eosinophilia of the cytoplasm, but tissue destruction was not visible. On day 1, many neurons (>50%) showed typical morphologic changes of ischemic cell death, such as eosinophilia of the cytoplasm and irregularly shaped nuclei (Fig. 3b). Severe tissue destruction resultant from infarcts was observed mainly in Rexed lamina 7 in gray matter 3 days after resuscitation. Vacuole formation and infiltration of inflammatory cells were also found in the infarction. These cellular reactions were evident at day 3, and it became most obvious on day 7. Throughout the experimental period, ischemic changes of the large motor neurons in the ventral horn (Rexed laminae 8 and 9) were not clearly observed. It was 12 hrs after resuscitation when FJB-positive neurons were detected, particularly in the dorsal horn (Rexed laminae 2–4). The medium-sized neurons in the intermediate gray matter were clearly stained with FJB (Fig. 3, j–l, n, and o). Neuronal cell death was observed in the Rexed laminae 2–7 at 12 hrs to 7 days after resuscitation (Fig. 3). Interestingly, in contrast to neurons in the dorsal horn and intermediate gray matter, most of the large motor neurons in the ventral horn (Rexed laminae 8 and 9) seemed intact and were not labeled with FJB at any time point (Fig. 3, i and p). The number of FJB-positive neurons decreased on day 7 because the degenerative neurons in the gray matter were lost. With TUNEL staining of sections from group C rats, most small neurons (>80%) in the dorsal horn were stained brown 12 hrs after resuscitation and became more prominent at 1 day and 3 days. Large motor neurons in the ventral horn were not labeled with TUNEL at any time point (data not shown).

**Necrosis-Like Neuronal Cell Death in the Medium-Sized Neurons in the Intermediate Gray Matter of the Lumbar Spinal Cord.** In hematoxylin and eosin staining, medium-sized neurons in the intermediate gray matter in group C rats showed strong eosinophilia with enlargement of their cell bodies at day 1 (red neurons) (Fig. 4b). Nuclei were lost with hematoxylin staining (“ghost” neurons) 7 days after resuscitation (Fig. 4c).

Electron microscopy examination provided ultrastructural evidence of the collapse of organelles in damaged neurons in the intermediate gray matter of the lumbar spinal cord. The neurons in control animals showed normal cellular architecture with pyramidal cell bodies, clear cell and nuclear membranes, and mitochondrial normal morphology (Fig. 4, d and g). In group C rats, cell bodies were markedly increased in size, and cytoplasmic electron density increased on day 1. Necrosis-like changes were confirmed in the neurons in the intermediate gray matter on the basis of swollen mitochondria with disorganized cristae, dilated endoplasmic reticulum, and an increase in the number of lysosomal-like deposits. Disruption of cell membranes was also observed, but the nuclear membrane was preserved (Fig. 4, e and h). Severe destruction of organelles was more obvious, and nuclear and cytoplasmic disintegration and membrane breakdown were more apparent, on day 7. Electron density was increased in both the cytoplasm and nuclei (Fig. 4, f and i). These features were characteristic of necrotic cell death, as previously reported (28, 29).

**Demyelination in the White Matter of the Lumbar Spinal Cord.** In group A rats, there were no remarkable changes observed, and a few vacuoles in group B rats were seen in the ventral white matter in two rats but never detected in other areas. In contrast, remarkable and severe ischemic changes were observed in group C rats. Tissue destruction was observed from day 1 after resuscitation as myelin vacuolization. This ischemic change, which was considered to be demyelination, was more numerous in the ventral and ventrolateral white matter and became more severe as time passed (Fig. 5, a–d: ventrolateral white matter, e–h: ventral white matter). In electron microscopy analysis (Fig. 5, i–k), normal axonal structure and distribution were observed in control animals (Fig. 5i). In contrast, massive axonal swelling was detected in animals on day 1 (Fig. 5j), and it was more prominent on day 7 (Fig. 5k). Degenerating axons with disintegrating myelin sheaths and empty space between the myelin sheath and axoplasm were observed. Semiquantification of demyelination was performed using Scion Image software. In groups A and B, the percentage of stained area decreased...
slightly on day 7, but there was no significant difference in comparison with control rats (data not shown). Semiquantification of demyelination in each area in control and group C rats is shown in Figure 5m. Vacuolation was widespread and prominent in the ventral and ventrolateral white matter in group C animals, and the demyelination was significantly progressed in a time-dependent manner. On the contrary, vacuolation in the corticospinal tract was relatively mild in comparison with the other two areas examined throughout the observation period, and a significant difference was found only at day 7 (p < .05) as compared with the control.

**DISCUSSION**

In the present study, we reconfirmed the vulnerability of the CA1 region of the hippocampus possesses to ischemia-induced damage. As clarified with FJB and TUNEL staining (Fig. 2), the neuronal cell death was seen in all the three groups and was indicative of apoptotic cell death (i.e., delayed neuronal cell death), as described previously (25–27). These results suggest that the CA1 region of the hippocampus is highly sensitive and vulnerable to global ischemia, but the severity of the global ischemic event does not influence the time course of cell death.

In contrast, the sensitivity and vulnerability of the spinal cord to global ischemia was completely different to that of the brain, and the time course of cell death was also markedly different for the same severity of global ischemia. In group A and B rats, no FJB- or TUNEL-positive cells were seen in gray matter, and demyelination was not detected at any time point; at the same time, many FJB- and TUNEL-positive cells were detected in the CA1 region of the hippocampus. Also, no group A or B rats showed a persistent motor deficit, and all animals recovered motor function within 6 hrs. However, in group C rats, severe tissue destruction and persistent hind-limb paralysis were observed (Fig. 1D). FJB- and TUNEL-positive cells were detected as soon as 12 hrs after resuscitation, mainly in the dorsal horn and intermediate gray matter (Fig. 3), yet no ischemic change was detected in the CA1 region at that time. Infarction (which was never observed in the CA1 region) was clearly observed in the intermediate gray matter 3 days after resuscitation. The infarcted area was infiltrated with many mononuclear cells and necrotic neurons (i.e., eosinophilic red neurons and ghost neurons) (Fig. 4, a–c). Ultrastructural evidence also indicated necrotic neurons in the intermediate gray matter, including mitochondrial swelling, endoplasmic reticulum dilatation, electron-dense deposit, and disruption of cell and nuclear membranes (Fig. 4, d–i).

These results demonstrate that the brain and spinal cord follow different time courses of cell death after the same severe global ischemic insult. Also, these findings suggest that the spinal cord has a higher tolerance to ischemia than the brain. However, it seems that spinal cord damage occurs much faster than brain damage when the severity exceeds its limits. Necrotic cell death was observed in damaged neurons in the intermediate gray matter of the lumbar spinal cord, whereas most of the damaged neurons in the CA1 region of the hippocampus showed apoptotic cell death.

Contrary to our expectations, most of the large motor neurons in the ventral horn seemed to survive (Fig. 3p), although most of these group C animals showed paraplegic motor deficits. However, demyelination in the white matter was prominent in group C (Fig. 5). From these results, it is suggested that the motor deficit was caused not only by degeneration of gray matter but also by demyelination of white matter. Our observation is consistent with previous studies (30) that observed neuronal cell death in the dorsal horns and intermediate gray matter and also recognized the hind-limb paralysis after spinal cord ischemia. Some previous studies have described white matter injury after spinal cord ischemia and suggest that white matter degeneration is an important mechanism in ischemia.
induced paralysis (31, 32). These reports, including our studies, suggest that the paraplegia after global ischemia might be caused by spinal cord damage.

In most of the studies of ischemic injury in the central nervous system in human and animal ischemia models, the brain and spinal cord were investigated separately. Ischemic damage of the spinal cord is usually studied with spinal cord ischemia models (19, 30, 33, 34). There have been a few studies that described a motor deficit, like paraplegia, after cardiac arrest (35–37), but none investigated and examined spinal cord damage after global ischemia. Spinal cord damage after global ischemia to date is poorly understood, although brain damage has been extensively studied.

The effect of ischemia on the spinal cord has been studied using various spinal cord ischemia models. However, the clinical situation of cardiac arrest/CPR is much more complicated than simple spinal cord ischemia alone. Many intra-ischemic and postischemic factors, which may influence the neurologic outcome, are likely to be neglected in such models. For these reasons, our model resembles the clinical situation closely, and we believe that this is a very useful and suitable model to investigate more accurately the effects of simultaneous ischemic damage to the brain and spinal cord.

We have demonstrated that severe global ischemia causes spinal cord damage and that the motor deficit after global ischemia might be caused, primarily, by spinal cord damage. A limitation of this study is that we did not examine other segments of the spinal cord (cervical and thoracic spinal cord) and brain (motor cortex) that could cause motor deficit–like hind-limb paralysis. Therefore, further study will be necessary to determine why induction of neuronal cell death occurs differently in the brain and spinal cord. However, to our knowledge, there

Figure 4. Histologic (a–c) and ultrastructural (d–i) observation of necrotic neurons in intermediate gray matter of the lumbar spinal cord in control (a, d, g) and at 1 (b, e, h) and 7 (c, f, i) days after resuscitation in group C rats. Medium-sized neurons in the infarcted area (Rexed laminae 4–7) show necrotic change as strong eosinophilia (red neurons, arrowheads) at day 1 (b) but not in the control (a). After day 7 (c), nuclei lost hematoxylin staining (ghost neurons, arrow). Cell body, mitochondria (M), and endoplasmic reticulum (ER) in the neuron of the control animals (d, g). The cell body is markedly increased in size, and cytoplasmic electron density increased on day 1 of a group C rat (e). Swollen mitochondria with disorganized cristae and increased numbers of lysosomal-like deposits (L) were observed (h), and the nuclear membrane seemed intact. A necrotic neuron is noted at day 7 in a group C rat (f). Severe swelling of organelles and nuclear and cytoplasmic disintegration at day 7 is apparent, along with membrane breakdown (f, i). Scale bars: 20 μm in a–c, 5 μm in d–f, and 0.5 μm in g–i.

Figure 5. Demyelination in ventral (a–d and i–k) and ventrolateral (e–h) funiculi of the lumbar spinal cord of control and group C rats in the control (a, e, i) and at 1 (b, f, j), 3 (c, g), and 7 (d, h, k) days after resuscitation with histologic (a–h) and ultrastructural (i–k) observation. Vacuolation is widespread and became more prominent in the ventral and ventrolateral funiculi as time passed (scale bars: 20 μm in a–h). Normal axonal structure and distribution were observed in control animals. Degenerating axons with disintegrating myelin sheaths were seen, and empty space was observed between the myelin sheath and axoplasm in group C rats (scale bars: 5 μm in i–k). Schematic representation of the lumbar spinal cord and calculated areas (l). Semiquantification of demyelination in group C using Scion Image software (m). There were significant differences between control and group C at day 7 (p < .05) in the corticospinal tract, at day 3 (p < .01) and day 7 (p < .001) in the ventrolateral white matter, and at day 1 (p < .001), day 3 (p < .001), and day 7 (p < .001) in the ventral white matter of lumbar spinal cord (Dunnet post hoc test).
has been no report that described and compared damage in both the brain and spinal cord after global ischemia in detail. Also, this is the first laboratory study that suggests that the motor deficit resultant from global ischemia may be caused primarily by spinal cord damage.

In the clinical situation of severe global ischemia, strategies for the prevention of brain damage have been examined intensively. Little attention, however, has been paid to potential spinal cord damage. However, spinal cord damage may occur much faster and be more severe than brain damage after severe global ischemia. Because motor deficits, such as hind-limb paralysis, result in a marked decrease in the quality of life, we should take into consideration that the spinal cord might have acute and severe damage, potentially as important as possible brain damage, under global ischemic conditions.

CONCLUSION

The present study demonstrates the different features of neuronal damage of the brain and spinal cord. Our combination model of hemorrhagic shock and cardiac arrest caused acute neuronal cell death in the lumbar spinal cord, characterized by apoptosis and necrosis, and delayed neuronal cell death in the hippocampus, characterized by apoptosis. Neuronal damage in the gray matter and demyelination in the white matter of the lumbar spinal cord might be responsible for hind-limb paralysis after global ischemia. The importance of neuronal damage and potential motor deficits of the spinal cord should be considered when treating global ischemia patients.

REFERENCES


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