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MAGNETIC RESONANCE IMAGING AND PATHOLOGIC STUDIES ON LATERAL FLUID PERCUSSION INJURY AS A MODEL OF FOCAL BRAIN INJURY IN RATS

BY

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ABSTRACT

In this study, morphologic changes in brain lesions initiated by moderate lateral fluid percussion injury in rats were investigated chronologically using high-resolution magnetic resonance imaging (MRI) and histopathologic methods. Rats were subjected to moderate fluid percussion injury (average 2.80±0.48 atmospheres) over the exposed dura overlying the right parietal cortex. MRI obtained *in vivo* were compared with corresponding pathologic findings at 1, 6, and 24 h and at 3, 6, 14 and 80 days after injury. T2-weighted images showed scattered low-signal intensity in the injured cortex within a few hours after injury, whereas histologic findings revealed intraparenchymal hemorrhages. T2-weighted images of the ipsilateral cerebral cortex and/or corpus callosum showed a high-signal-intensity area 4 h after injury. The high-signal-intensity area became largest in size between 6 and 24 h, then declined gradually, and almost disappeared 14 days after injury. Histologic examination revealed pyknosis, retraction of the cell body of neurons with vacuolated neuropil in the corresponding regions 6 and 24 h after injury, and cystic necrosis 14 days after injury. The location and extent of these pathologic changes were depicted accurately by MRI *in vivo*. In the hippocampus, pyknosis and retraction of the cell body of pyramidal neurons were observed on the injured side 24 h after injury, and the number of neurons in the CA1 and CA2-CA3 regions decreased significantly on the same side by 14 days after injury. It is concluded that morphologic changes in the brain following experimental traumatic brain injury in rats are detectable *in vivo* by high-resolution MRI, and that MRI may be useful for the evaluation of treatment effects in experimental brain injury.

Key words: Focal brain injury, Fluid percussion injury, Magnetic resonance imaging, Rat

INTRODUCTION

Experimental models of traumatic brain injury produce clinically relevant pathologic lesions by the application of mechanical forces. A wide array of experimental models of traumatic brain injury remains necessary to study the mechanism of corresponding brain injury in humans (Povlishock et al. [1]). It has recently become difficult, however, to conduct experimental studies on brain injury using

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large animals or subhuman primates. Although the rat is inferior to larger animals or primates as a model of human head injury, the use of laboratory rats provides some advantages such as easy handling during experiments and economical use of expensive radioisotopes and drugs because of their low body weight (Dixon et al. [2]). Several models of mechanical brain injury have been developed (Gennarelli [3]), including devices that accelerate or rotate the skull, and that cause impact injury to the intact cranium (Marmarou et al. [4]; Foda and Marmarou [5]; Nawashiro et al. [6]), fluid percussion injury (Dixon et al. [2]; McIntosh et al. [7]; McIntosh et al. [8]; Yoshino et al. [9]; Yamakami and McIntosh [10]; Shibata et al. [11]; Yamaki et al. [12]; Qian et al. [13]; Qian et al. [14]), and injuries by suction or pneumatic impact to the exposed dura (Sutton et al. [15]; Katayama et al. [16]). Among those available, the fluid percussion injury model in the rat reproduces many features of head injury smilar to those observed in other models and species, and to the biochemical, physiologic, neurologic, and pathologic responses in humans (Dixon et al. [2]; McIntosh et al. [7]; Yamakami and McIntosh [10]; Yamaki et al. [12]; Qian et al. [14]). This model also presents alterations in intracranial pressure and EEG activity, both focal and global alterations in cerebral blood flow and metabolism, disruption of the blood-brain barrier, development of regional cerebral edema, neuronal injury in hippocampus (Qian et al. [14]; Cortez et al. [17]; Hicks et al. [18]), expression of neuronal stress proteins and immediate-early genes such as *c-fos* (Raghupathi et al. [19]), neuromotor deficits, and cognitive dysfunction.

Our previous study characterized pathophysiologic and morphologic responses to moderate midline fluid percussion injury in rats, suggesting that this model is useful for studying the mechanism of experimental diffuse brain injury (Qian et al. [14]). Recently, Iwamoto et al. [20] reported that moderate lateral fluid percussion injury produced focal brain lesions in rats. Focal brain injury is differentiated from diffuse brain injury and is important in understanding secondary brain damage caused by hemorrhage, ischemia, and edema. Nevertheless, few *in vivo* chronological studies on traumatic focal brain lesions have been performed.

Magnetic resonance imaging (MRI) has proved to be highly effective in detecting both primary lesions and secondary pathophysiologic changes. Secondary changes, such as brain edema and ischemic processes, accelerate brain damage in head-injury patients. MRI offers a means to assess several pathophysiologic parameters that are directly related to the quantities and state of hemoglobin and water in brain tissue. The usefulness of MRI in experimental studies with small animals has also been reported (Hanstock et al. [21]). At present, MRI seems to be more suitable for studying focal brain injury than diffuse brain injury in rats in terms of resolution. The purpose of the present study was to investigate *in vivo* the chronological changes in focal brain lesions initiated by moderate lateral fluid percussion injury in rats by means of high-resolution MRI. Parallel histopathologic examination was performed to confirm these MRI findings.

Materials and Methods

Animal preparation

Female Wistar rats weighing from 350 to 500 g were anesthetized with ketamine hydrochloride (50 mg/kg, i.m.). Each rat was positioned in a stereotaxic frame, and a 4-mm-diameter burr hole was drilled over the right parietal cortex between the bregma and lambda. Body temperature

was maintained between 36 and 37°C with a heating lamp. During surgical preparation and throughout the experiments, all wounds were infiltrated with 2.0% lidocaine hydrochloride. Rats were allowed to breathe spontaneously throughout all surgical procedures.

Fluid percussion injury

The fluid percussion injury device has been previously described in detail (Qian et al. [13]). In brief, it consists of a cylindrical reservoir with a pressure transducer connected to a personal computer. A 10-cm-long plastic tube connected to the reservoir was placed over the burr hole and fixed with Aron-alpha cement (Konishi Co., Ltd., Osaka, Japan). The rats were divided into two groups: a sham-operated group (n=6) and a group exposed to moderate lateral fluid percussion brain injury (n=56). While the rat was maintained under general anesthesia with ketamine hydrochloride, injuries were induced by dropping a metal pendulum from predetermined heights to strike the piston of the device, producing different extracranial pressure pulses expressed in atmospheres (atm). Moderate lateral fluid percussion injuries were caused by pulses between 1.98 and 3.54 atm (average 2.80±0.48 atm) on the 4-mm-diameter area, with a mortality rate of 19.6% in this study. Rats that died from this procedure were excluded from the following MRI and pathologic studies.

MRI studies

MRI studies were carried out with a 4.7-Tesla experimental imager/spectrometer system (Unity plus SIS 200/330, Varian, PaloAlto, Ca, USA) equipped with a 33-cm horizontal bore magnet (Oxford Instruments, England) and with a gradient strength of 50 mT/m. For radio frequency (RF) transmission and detection, a 4-cm-diameter homogeneous quadrature coil was used. The MRI experiments were performed on rats anesthetized with ketamine hydrochloride 1, 4, 6, 18 and 24 h and 2, 3, 6, 14 and 80 days after injury (Table 1). Fixation of the interaural line was achieved by inserting acrylic ear plugs into the external auditory canals. Rats were anesthetized with 1% isoflurane in oxygen using a face mask, and body temperature was maintained at 36 and 37°C by passing warm water through a heat exchanger machined into water blankets while the rat was inside the magnet. The rats were placed in the center of a magnetic field in a supine position. Manual shimming was performed to improve magnetic homogeneity before the

Table 1. Distribution of MRI and Histopathology

	Sham	Time after Injury									
	Control	1h	4h	6h	18h	24h	2D	3D	6D	14D	80D
T1-weighted image	3	8	8	9	3	6	5	6	4	5	3
T2-weighted Image	3	8	8	9	3	6	5	6	4	5	3
MRI with histopathology	3	3	—	3	—	3	—	3	3	5	3
Histopathology without MRI	3	—	—	—	—	—	—	—	—	5	—

image data collection. Typical images were obtained with the following acquisition. T1-weighted spin-echo (SE) images (TR/TE ms=500/20) and T2-weighted SE images (TR/TE ms=2000/80) with two signal acquisitions were done. Images were obtained from a 2-mm-thick coronal section using a 4-cm field of view with a 128×128 matrix zero-filled to 512×512. A total of 48 rats, including 3 sham-operated controls, received 60 serial MRI examinations. The percentage of the high-signal-intensity area relative to the total area of the brain slice on T2-weighted images was calculated using image analysis software (NIH Image) on a personal computer to evaluate traumatic brain edema.

Histologic examination

Rats (n=34) were anesthetized with sodium pentobarbital and fixed by transcardiac perfusion with 10% buffered neutral formalin at 1, 6, and 24 h and at 3, 6, 14 and 80 days after injury. Three sham-operated control rats and five injured rats without MRI examinations were included in this group. The number of rats killed at each time point is shown in Table 1. The brain was removed and examined macroscopically, and coronal sections of the injured cortex and hippocampus 4 mm posterior to the bregma were prepared for microscopic examination using hematoxylin and eosin (HE) and Klüver-Barrera (KB) staining. The total number of apparently normal and abnormal neurons (dark, shrunken, and elongated, or light and swollen) in the hippocampal pyramidal layer 14 days after injury were counted in the CA1 and CA2-CA3 sections by taking 5-μm-thick sections from five injured rats with MRI examination and five injured rats without MRI examination. Results were expressed as number of neurons per mm of the pyramidal layer. The areas of necrosis in the cortex shown by HE staining were calculated using image analysis software (NIH image) on a personal computer.

Statistical analysis

All results are presented as mean±SD. Statistical analysis was performed by using paired and unpaired t-test. Correlation between the two parameters was calculated by using linear regression analysis. A value of $p<0.05$ was taken as statistically significant.

Results

Appearances in MRI

In sham control rats, lateral ventricles were depicted as low- and high-signal-intensity areas on coronal T1-and T2-weighted MRI, respectively. Progression of the lesion in rats could be seen in the series of T2-weighted MRI. T1-and T2-weighted images obtained within 1 h after injury showed scattered low-signal-intensity areas, which were mostly localized in the cortex and corpus callosum directly under the impact site. With the exception of one rat, no high-signal-intensity area was detected until 4 h after injury. However, by 6 h after injury, a high-signal-intensity area was clearly demonstrated on T2-weighted images of the injured region of cortex in all rats (Fig. 1). The high-signal-intensity area was approximately twice larger than the diameter of the burr hole and largest in area between 6 and 24 h after injury (Fig. 2). During this period, the corpus callosum was involved in the high-signal-intensity area in most rats. The hippocampus was compressed by the enlarged high-signal-intensity area, but was not involved in the area in any rat (Fig. 1, C). This high-signal-intensity area gradually declined in size by 2 days after injury, although a high-signal area whose size was reduced to less than a half was still detected 6 days after injury (Fig. 1, D).

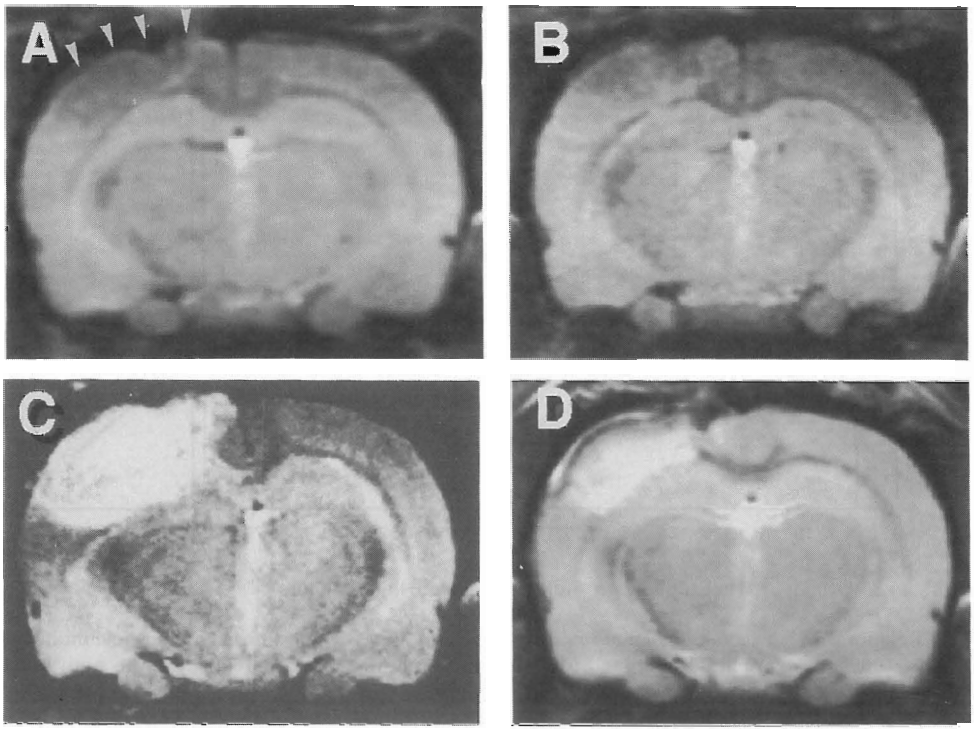


Fig. 1 Serial coronal T2-weighted MRI showing changes in signal intensity after moderate lateral fluid percussion injury in a rat. A: MRI obtained 1 h after injury. No high-signal-intensity area is seen. Arrowheads show the site of fluid percussion injury. B: MRI obtained 4 h after injury. A slight high-signal-intensity area is detected. C: MRI obtained 18 h after injury. A high-signal-intensity area is clearly seen in the cortex and corpus callosum under the impact site. The hippocampus is compressed by the high-signal-intensity area. D: MRI obtained 6 days after injury. The high-signal-intensity area is resolving but is still detectable.

The high-signal-intensity area almost disappeared by 14 days after injury (Fig. 3, D). Three rats received MRI examination on the 80th day after injury. The high-signal-intensity area was not recognized through T2-weighted images in these rats. Areas with a high-signal-intensity in the early stage were replaced by cerebrospinal fluid. Enlargement of the lateral ventricles and cisterns was also observed.

Histologic assessment

Histologic studies revealed intraparenchymal hemorrhages at the border between the gray and white matter directly under the impact site and also in the corpus callosum ipsilateral to the injury at 1 h after injury. Pyknosis and retraction of the cell body of the neurons were observed in the injured cortex as early as 1 h after injury. These changes corresponded to a scattered low-signal-intensity area directly under the impact site observed 1 h after injury on T2-weighted images. Numerous dilated vessels and small hemorrhages were observed in the same area (Fig. 3, I). At 6 h after injury, histologic examination revealed more pronounced pyknosis and retraction of the cell body of the neurons with vacuolated neuropil in the cortex beyond the impact site, which corresponded to the high-signal-intensity area of

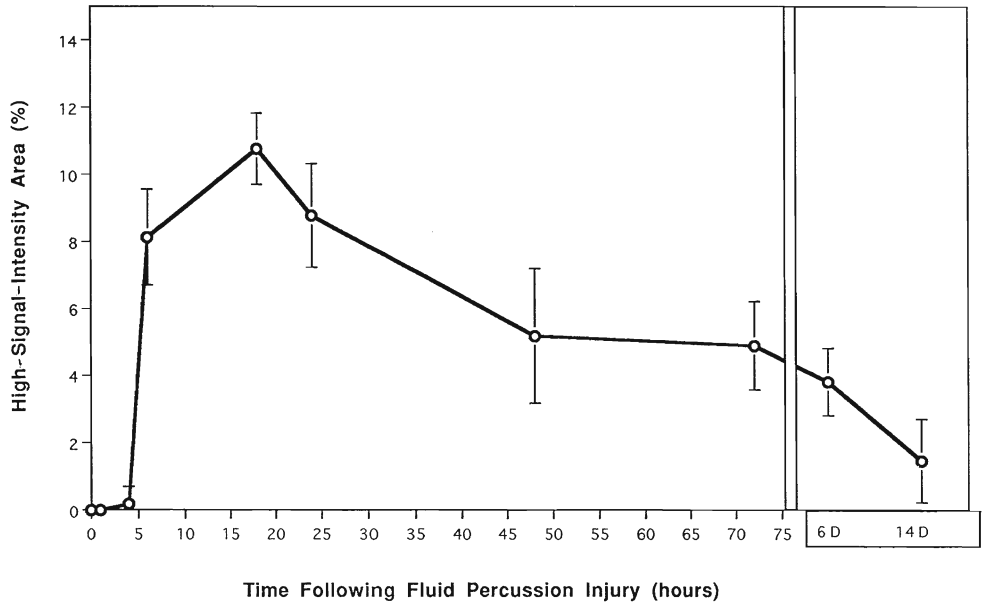


Fig. 2 Relationship between high-signal-intensity area ratio (high-signal-intensity area/ whole brain area × 100%) on coronal T2-weighted MRI and time following fluid percussion brain injury. The peak occurred between 6 and 24 h after injury.

the T2-weighted image (Fig. 3, J). The area of edematous changes was larger than the area of impact burr hole by 2 mm in maximum diameter and limited to the ipsilateral cortex or/and corpus callosum. By 24 h after injury, the area of injured cortex became necrotic with more severe edema, and part of the area was separated from the surrounding tissue by its pale staining. In the central area of the injury, pyknosis and retraction of the cell body of the neurons and vacuolation of the neuropil were severe and corresponded to the high-signal-intensity area of the T2-weighted image (Fig. 3, K). At the periphery of the injured area, neuronal change and vacuolation was mild, and normal neurons could be observed as well. By 14 days after injury, the lesion became an area of cystic necrosis with a few remnant pyknotic neurons and scattered lipid-laden macrophages (Fig. 3, L). The extent of necrosis corresponded to the size of the high-signal-intensity area. Histologic changes were similar between animals studied using both histology and MRI and those studied with histologic measures alone 14 days after injury. Although MRI revealed no signal changes in the hippocampus, pyknosis and retraction of the cell body of pyramidal neurons were observed 24 h after injury, and the number of surviving neurons on the injured side was decreased to 132±22 in the CA1 section and to 128±16 in the CA2-CA3 sections by 14 days after injury (Fig. 4), which were significantly lower than the contralateral values (173±10 and 164±7, respectively) (paired t-test, $p<0.01$) and the control values on the left side (187±10 and 168±6, respectively) (unpaired t-test, $p<0.01$) (Fig. 5). There was a close correlation between the rate of decrease in the number of neurons in the CA1 and CA2-CA3 regions and the area of necrosis in the cortex (Fig. 6). The correlation coefficient

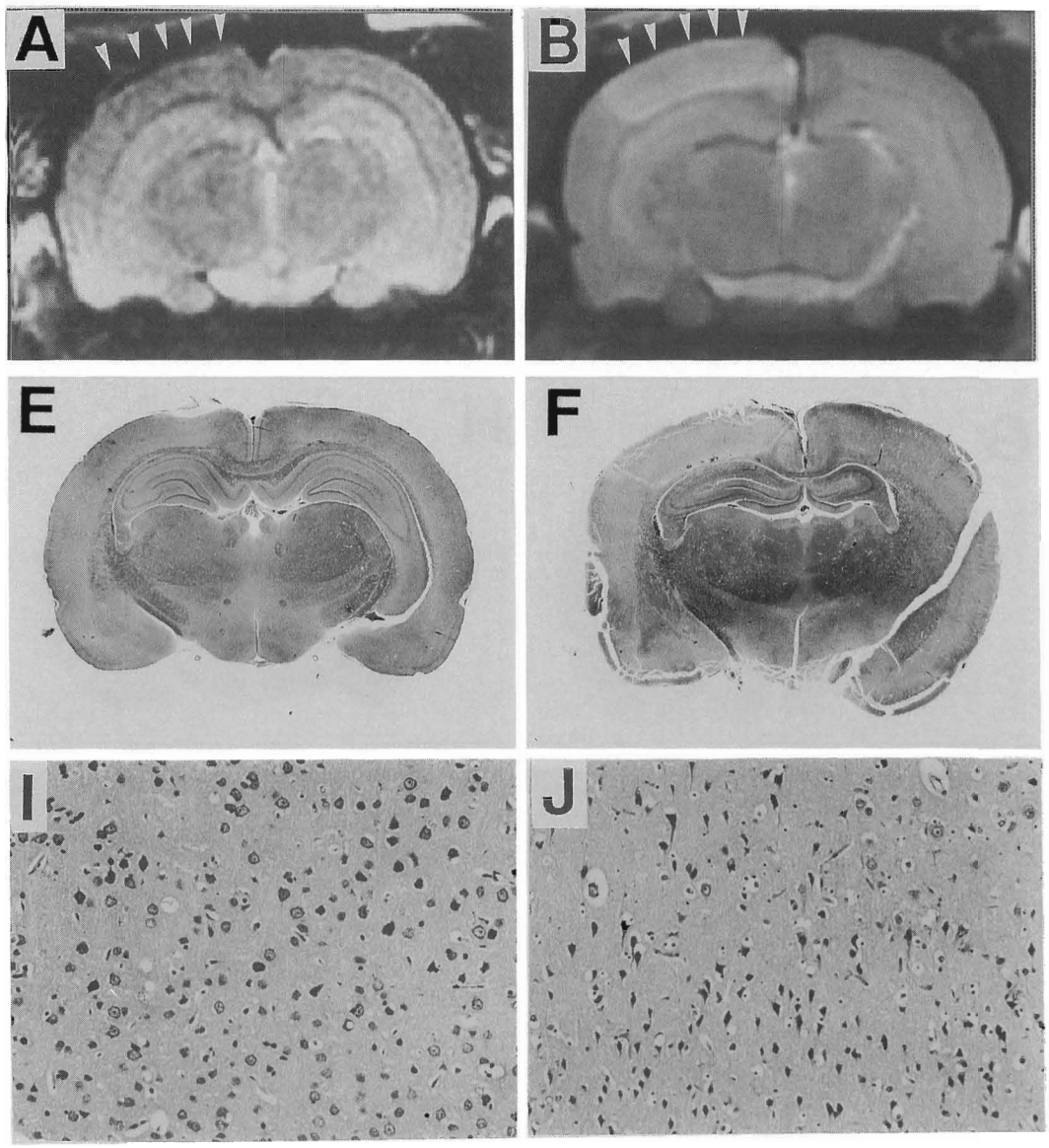
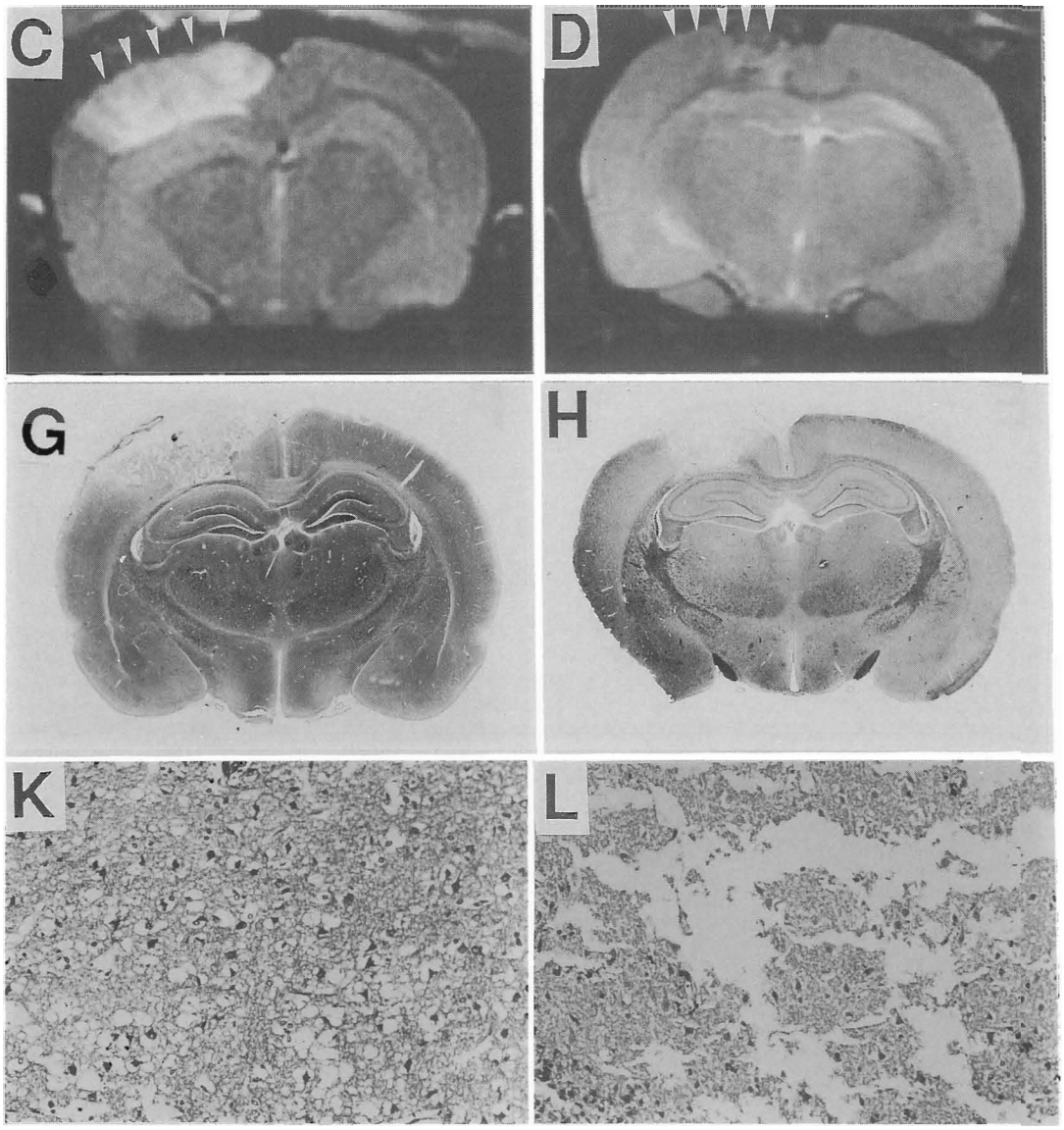


Fig. 3 T2-weighted MRI (A, B, C, D) and histologic views of injured cortex (E, F, G, H, × 6; I, J, K, L, × 125, HE stain). They are obtained 1 (A, E, I), 6 (B, F, J) and 24 (C, G, K) h and 14 (D, H, L) days after injury. Brain injuries were made on the right side of the rat brain, shown as the left side of all figures (arrowheads). One hour after injury, MRI showed a low- and iso-signal-intensity (A), while, microscopically, dark contracted neurons were observed in the cortex under the impact site (I). Six hours after injury, a high-signal-intensity area appeared in the cortex under the impact site (B) and macroscopically corresponded to pale zone of staining (F), in which pyknosis and retraction of the cell



body of neurons with vacuolated neuropil were evident (J). Twenty-four hours after injury, the high-signal-intensity area was enlarged and compressed the underlying tissue including the hippocampus (C). Microscopically, neurons were shrunken and surrounded by pronounced vacuolation of the neuropil in the center of the injured cortex (K). The lesion showed cystic necrosis (H) with a few remnant pyknotic neurons (L) 14 days after injury. The high-signal-intensity area was nearly resolved (D).

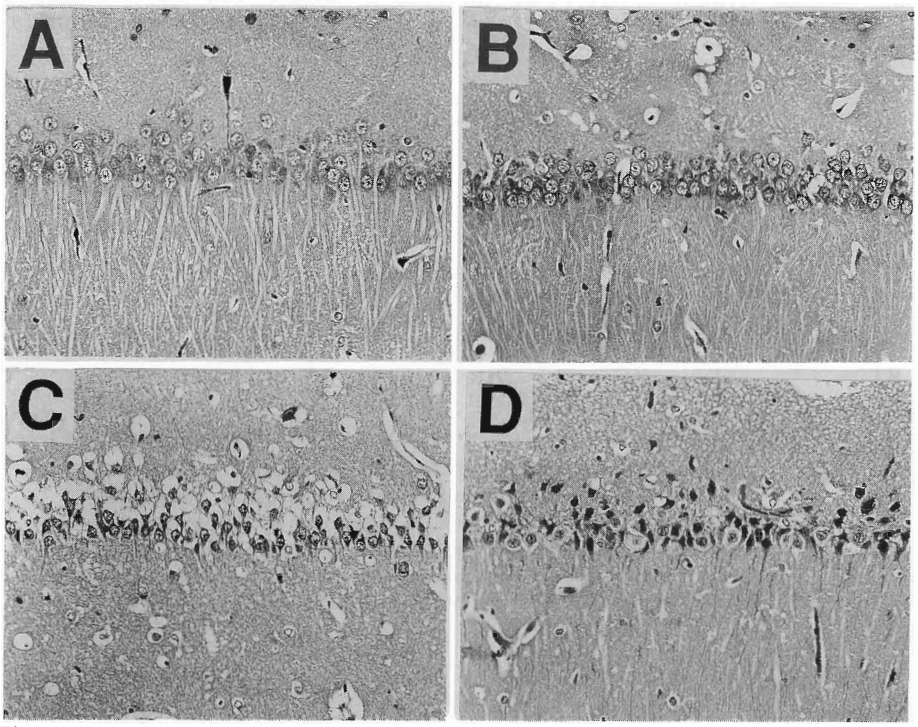


Fig. 4 Photomicrograph of CA1 area of the hippocampus on the injured side showing progressive neuronal damage in sham control (A), 1 h (B), 24 h (C) and 14 days (D) after injury. (HE stain. × 130).

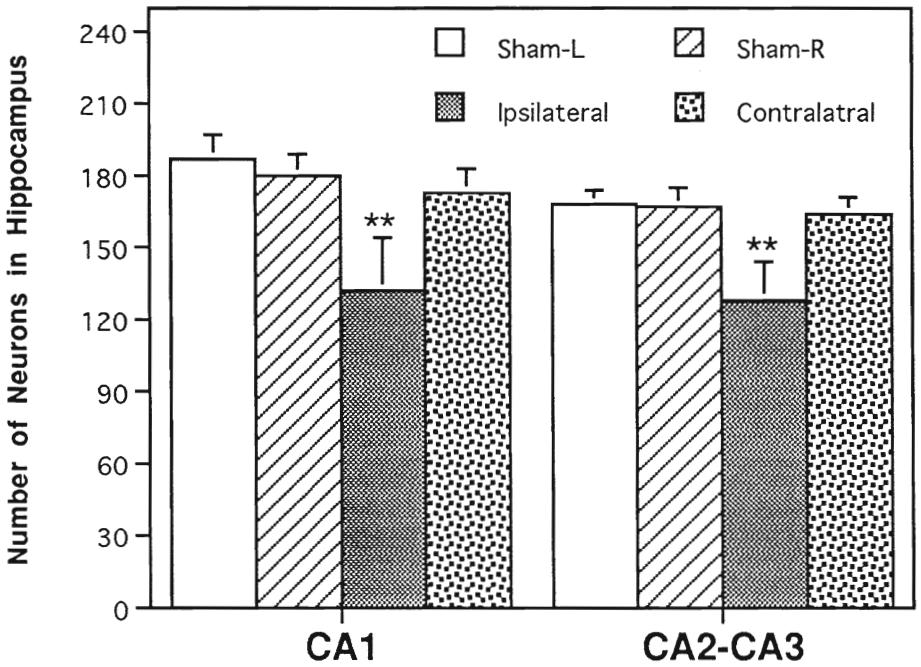


Fig. 5 Reduction in the number of neurons in areas CA1 and CA2-CA3 in the injured hemisphere, compared with those in sham controls (unpaired t-test, $p<0.01$) and in the contralateral hemisphere (paired t-test, $p<0.01$). The number of neurons was significantly decreased on the injured side.

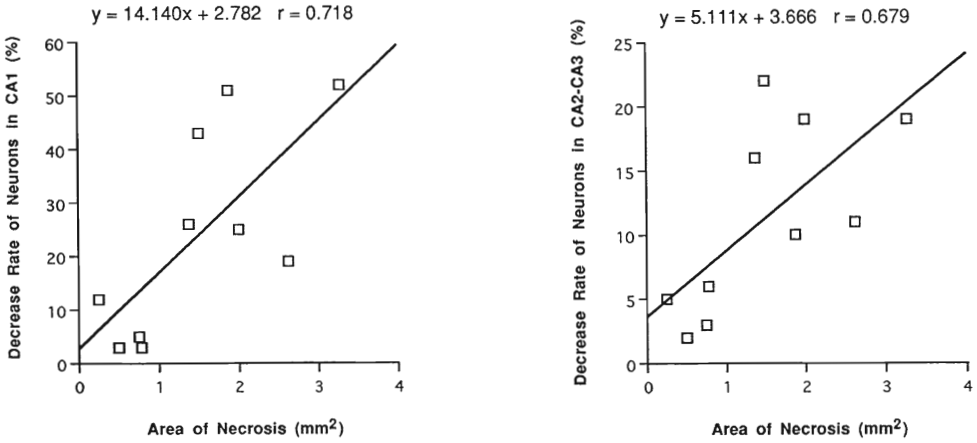


Fig. 6 Relationship between decrease rate in the number of neurons in the CA1 and CA2-CA3 regions and the area of necrosis in the cortex. Decrease rate = (A-B)/A×100%. A = Number of neurons on the contralateral side. B = Number of neurons on the ipsilateral side. Area of necrosis is expressed as mm^2. The correlation coefficient (r) was 0.718 for CA1 and 0.679 for CA2-CA3 regions.

(r) was 0.718 for the CA1 and 0.679 for the CA2-CA3 regions. No pathologic changes were seen in the other regions of the brain.

Discussion

Lateral fluid percussion injury model

A fluid percussion brain injury model using rats has been reported to be useful for studying pathophysiologic and morphologic responses to graded magnitudes of traumatic brain injury (Dixon et al. [2]; McIntosh et al. [7]). We chose a moderate grade of lateral fluid percussion injury generated by our original device in the present study, because this grade of injury constantly produced pathophysiologic responses and morphologic lesions in the injured hemisphere, although approximately 20% of the animals subjected to moderate injury with our device died as a result of the trauma.

Our previous data (unpublished observation) and other studies (Yoshino et al. [9]; Yamakami and McIntosh [10]; Shibata et al. [11]) demonstrated that local cerebral blood flow decreased, while local cerebral glucose utilization increased diffusely in most regions of the rat brain 1 h after moderate lateral fluid percussion injury. However, no morphologic abnormality occurred in the regions of the brain other than the cortex and hippocampus under the impact site in the present study. Thus, following moderate lateral fluid percussion injury, only focal lesions under the impact site were evolved morphologically and resulted in necrosis in the cortex and neuronal damage in the hippocampus, although cerebral blood flow and glucose metabolism responses occurred over a wide area of the brain. These findings clearly differ from those following midline fluid percussion injury, which produces diffuse axonal injury in the brain.

Chronological changes in MRI findings

In the present study, a high-signal-intensity area in the injured site on T2-weighted MRI appeared 4h after moderate injury and was largest in size between 6 and 24 h. This high-signal-intensity area

reflects both contusional lesions and cerebral edema caused by contusions, because the injured cortex appeared as a scattered low-signal-intensity area in T1-and T2-weighted images 1 h post-injury, and also because the high-signal-intensity area gradually resolved after 24 h and progressed to cystic necrosis. Sutton et al. [15], in their histologic study of cortical contusions in rats induced with a pneumatic impactor, demonstrated that edematous response was most prominent between 6 and 24 h after injury and that it resolved by 8 days after the insult. The time course of posttraumatic intensity changes observed with MRI in our study was similar to that of focal edema shown in their histologic findings.

Hanstock et al. [21], in their study of moderate fluid percussion-induced brain injury in rats, reported that T2-weighted images between 1 and 4 h after trauma did not show any regions of altered signal intensity in the injured site, but diffusion-weighted MRI images obtained as early as 1 h after injury demonstrated a decrease in signal intensity in the region. They also showed that diffusion-weighted images developed no regions of hyperintensity during the first 4 h after moderate trauma, suggesting no occurrence of cytotoxic edema (movement of extracellular fluid into cells); furthermore, they found that the degree of edema in the injured cortex was four times greater than that observed in the hippocampus by calculating the apparent diffusion coefficients, and that the difference between injured cortex and hippocampus was most prominent by 4 h after trauma. Baskaya et al. [22], in their studies using a specific gravity method, also showed that posttraumatic edema occurred significantly not only in the injured and adjacent cortices but also in the ipsilateral hippocampus between 6 and 72 h after injury in the controlled cortical-impact rat model. In our study, the hippocampus was not involved in the high-signal-intensity area on T2-weighted images. This difference may be due to the fact that total water increase in the hippocampus is too slight to be detected on T2-weighted images. It remains controversial which form of edema, cytotoxic or vasogenic, occurs predominantly during the first 4 h after traumatic brain injury. For further investigation, it is necessary for us to use diffusion-weighted MRI to differentiate vasogenic from cytotoxic edema in the acute stage following injury, because diffusion-weighted MRI is a valuable tool for determining information about the contribution of water in the cerebral cortex and hippocampus.

Correlation between MRI and pathologic findings

T1-and T2-weighted images obtained 1 h after injury showed scattered low-signal-intensity areas in the cerebral cortex and corpus callosum under the impact site in most rats, which corresponded to hemorrhages observed histologically. MRI, especially T2-weighted images, accurately depicted edematous changes as well as intraparenchymal hemorrhages *in vivo*, and these were verified later by histopathologic examination. Progression of high-signal-intensity areas, demonstrated by T2-weighted images of the cerebral cortex under the impact site, to subsequent necrosis in our study seems to have been caused by both primary contusion and perifocal ischemia in combination with biochemical changes. According to the study of Sutton et al. [15], the contused cortex is exposed to a pronounced level of ischemia immediately after the insult and to subsequent low rates of glucose metabolism during the chronic stage. These authors suggested that the mechanisms underlying edema formation, metabolic

dysfunction, and neuronal death following contusional injury may include not only an increase in the release of excitatory amino acids but also the superimposed component of cerebral ischemia occurring concurrently with the contusion. Thus, it is possible, using high-resolution MRI, to demonstrate progressive pathologic changes *in vivo* of experimental brain injury in rats. MRI studies may also be useful for evaluating the effect of medical treatment on experimental brain injury.

Neuronal changes in hippocampus

It has been reported that following experimental traumatic brain injury neuronal damage in the hippocampus ipsilateral to the injury occurred (Nawashiro et al. [6]; Katayama et al. [16]; Cortez et al. [17]; Hicks et al. [18]). These authors pointed out that neurons only in the CA3 or in the CA2-CA3 regions were selectively damaged following cortical concussion or contusion. Katayama et al. [16] suggested that excitatory amino acids were responsible for the selective vulnerability in CA3 neurons following controlled cortical impact injury. Cortez et al. [17] reported neuronal cell injury in the CA2-CA3 region ipsilateral to the moderate lateral fluid percussion injury, and indicated that this neuronal injury in the hippocampus serves as a useful marker to assess the effect of pharmacological treatment of experimental brain injury. In our study, neuronal damage occurred in both the CA1 and CA2-CA3 regions. It is unknown why there is a discrepancy between their results and ours, but a possible explanation may be the difference in the impact site or in the methods for producing injury.

Apnea occurred in the surviving rats from a few to 20 s after the moderate fluid percussion injury. Although we have no data on blood gases and blood pressure in all rats used for histologic examination in the present study, our previous studies (Qian et al. [14] and unpublished data) showed that blood pressure increased transiently by about 30% of baseline, but returned to baseline levels within 30 s after moderate fluid percussion injury, and no significant changes in the concentration of blood gases from baseline values were observed in the surviving rats during the experimental procedure. Also, there was no significant decrease in the number of neurons on the contralateral side. Therefore, it is unlikely that a post-injury respiratory disorder might have been responsible for the neuronal damage in the hippocampus on the injured side.

Our chronological MRI studies clearly showed that the injured cortex showing a high-signal-intensity area enlarged and compressed the adjacent hippocampus over a wide area when the swelling had reached its peak between 6 and 24 h after injury. The CA1 as well as CA2-CA3 regions might be influenced because of their anatomical proximity to the enlarged area. Neurons in the hippocampus may have been injured by this compression. Furthermore, our data demonstrated that the decrease in the number of neurons tended to depend on the extent of necrosis in the cortex of each rat. This finding suggests that neuronal damage in the hippocampus may be related to the degree of cortical injury. It is also likely that ischemia and/or increased release of excitatory amino acids are responsible for the decreased number of neurons in the hippocampus (Sutton et al. [15]; Cortez et al. [17]; Katayama et al. [16]; Faden et al. [23]; Katayama et al. [24]).

Conclusions

We demonstrated the chronology of focal brain lesions *in vivo* using MRI following lateral fluid percussion brain

injury in rats. Chronological changes of the *in vivo* images correlated well with histologic findings. Chronological morphologic changes in the brain following experimental traumatic brain injury in small animals are detectable *in vivo* by high-resolution MRI, which is useful in studying the changes in blood and brain water caused by primary and secondary damage and is potentially useful for evaluating the effects of treatment in experimental brain injury.

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