Traumatic Contusion of ICR Mouse Brain by FPI: ^{1}H MR Spectroscopic Study

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In vivo ^{1}H magnetic resonance spectroscopy (MRS) at 4.7 T was applied to investigate the cerebral metabolite changes of mice brain before and after experimental brain trauma. *In vivo* ^{1}H MR spectra were acquired from a voxel covering right parietal cortex in normal brain, used as control subjects. After experimental brain trauma using the fluid percussion injury (FPI) method, ^{1}H MR spectra were acquired from the same lesion three days after trauma. Metabolite ratios of the injured lesion were compared to those of controls. After trauma, N-acetylaspartate (NAA)/creatine (Cr) ratio, as a neuronal marker was decreased significantly versus controls, indicating neuronal loss. The ratio of NAA/Cr in traumatic brain contusion was 0.90±0.11, while that in normal control subjects was 1.13±0.12 (P=0.001). Choline (Cho)/Cr ratio had a tendency to rise in experimental brain contusion (P=0.02). Cho/Cr ratio after trauma was 0.91 ±0.17 while that before traumas was 0.76±0.15. Cho/Cr ratio was increased and this might indicate a inflammatory activity. However, no significant difference of [(glutamate+glutamine) (Glx)]/Cr was established between experimental traumatic brain injury models and normal controls. Lactate (Lac)/Cr ratio was appeared as a sign of shifted posttraumatic energy metabolism and increased versus controls. These findings strongly suggest that *in vivo* ^{1}H MRS may be a useful modality for clinical evaluation of traumatic contusion and could aid in better understanding the neuropathologic process of traumatic contusion induced by FPI. In the present study, *in vivo* ^{1}H MRS was proved to be a useful non-invasive method for *in vivo* diagnosis and monitoring of posttraumatic metabolism in models of brain contusion.

Key Words : Magnetic resonance spectroscopy (MRS), Trauma, Fluid percussion injury (FPI)

INTRODUCTION

In vivo ^{1}H magnetic resonance spectroscopy (MRS) is a noninvasive method that allows *in vivo* examination of the brain biochemistry[1]. It represents a novel approach to directly assess *in vivo* brain levels of specific chemicals of interest, such as N-acetyl aspartate (NAA), creatine (Cr), choline (Cho), myoinositol (Ino), glutamate (Glu), and glutamine (Gln), gamma-aminobutyric acid (GABA), which are involved in key physiological brain processes, and possibly implicated in the pathophysiology of psychiatric disorders[2]. The usefulness of localized *in vivo* ^{1}H MR spectroscopy has been demonstrated in many studies of the brain and its disorders, e.g., in hepatic encephalopathy, Alzheimer's, Huntington's, and Parkinson's diseases, acute traumatic brain injury, tumors, and dementia[3-6].

Fluid percussion injury (FPI) is a well-characterized experimental model of traumatic brain injury in the rat and mouse[7]. It involves the injection of an extradural fluid pulse through a central, lateral, or parasagittal in-

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jury cannula transiently deforming the brain over 10 to 20 msec[8]. FPI results in pathologic excitatory amino acid release, edema, blood-brain barrier breakdown, focal contusion to the cortex directly below the injury site, injury to subcortical structures with some regions of cellular death, as well as neurological and behavioral sequelae[9].

The purpose of this study was to investigate the proton metabolic differences of parietal cortex with experimental brain contusion of ICR mouse induced by FPI compared to normal controls anesthetized with diazepam/xylazine and to test the possibility that ^{1}H MRS findings could provide neuropathologic criteria in the diagnosis and monitoring of traumatic brain contusion. Using image-guided, water-suppressed *in vivo* ^{1}H MRS with a 4.7 T MRI/MRS system, we evaluated the MRS measurement of the relative proton metabolite ratio between experimental brain contusion of ICR mouse and healthy control subjects.

MATERIALS AND METHODS

MRI/MRS studies of 10 ICR mice (22-26 g) were performed in the same brain lesion, right parietal cortex before and after FPI experimental brain contusion. Five mice were male and five mice were female. Anesthesia was induced by intramuscular injection with diazepam/xylazine (8/8 mg/kg) during MRI and MRS data collection.

1. Fluid percussion injury

For FPI procedure in Fig. 1, ten ICR mice were used and placed in a stereotactic head holder (Stoeling Co., Wood Dale, IL). The scalp was reflected and the skull exposed through a midline insicion. In Fig 2, using a high-speed drill a 2.5 mm diameter craniotomy was made on the skull centered over the right parietal cortex (2 mm from the sagittal suture, midway between the bregma and the lambda) leaving the dura intact[7]. After craniotomy, a plastic leur adapter was positioned over the exposed dura. Animals were secured in a stereotactic frame and received lateral FPI of moderate (2.0 atm) intensity by allowing a pendulum to strike the piston filled with sterile saline. Scalp was approximated with Nylon sutures.

2. ^{1}H MR Spectroscopy

All MRI and *in vivo* ^{1}H MRS experiments before and after FPI were performed on a 4.7 T MRI/MRS system with 3 cm vertical bore size (Varian, Unity Inova, Palo Alto, CA) with a 30 mm Millepede quadrature probe. And, for the studies after FPI, all experiments were carried out 72 hours after FPI for physiological equilibrium state. Localized single voxels (0.08 ml) centered

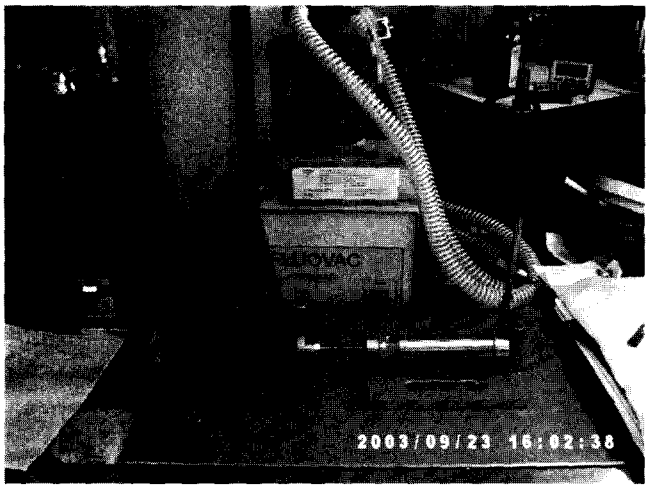

Fig. 1. A typical fluid percussion injury (FPI) device.

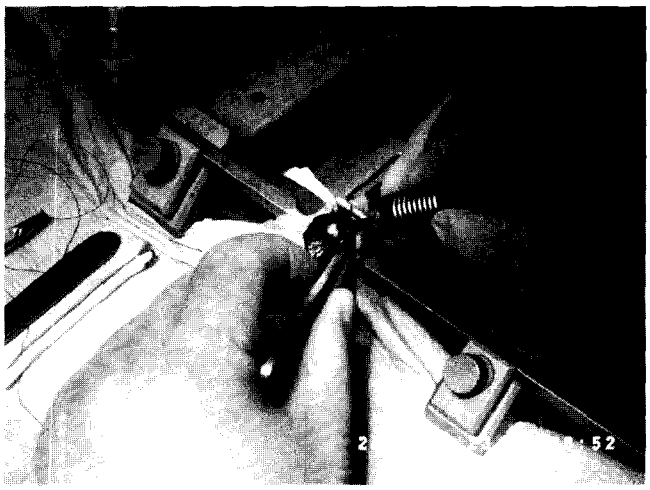

Fig. 2. Using a high-speed drill a 2.5 mm diameter craniotomy was made on the skull centered over the right parietal cortex leaving the dura intact.

on the volume of interest regions in the right parietal cortex including subcortical area were selected using T2-weighted MR imaging (TR, 1500 ms; TE, 60 ms). A stimulated-echo acquisition mode (STEAM) pulse sequence was used for localization and suppression of the water signal involved the use of a three-pulse chemical shift selective (CHESS) sequence[10]. Image-guided STEAM spectra were obtained with a TE of 20 msec[11], TR of 2000 msec, spectral bandwidth of 2500 Hz, and acquisition averages of 512.

3. Post-processing

Raw data were processed by MacSpec software (Medinus. Ltd. Seoul, Korea). Postprocessing involved the removal of residual water signal, correction if needed of the heavy eddy current, Lorenz-to-Gauss transformation, Gaussian line broadening of 1 Hz, zerofilling of 4 K, Fourier transformation, and zero-order phasing of the transformed spectrum. Any resulting spectra which contained the features of inadequate signal-to-noise ratio (SNR), outer volume contamination, distorted baselines, severe phase distortion due to the heavy eddy current, hardware artifacts, or inappropriate suppression of the water signal were regarded as unacceptable and excluded from data analysis. Peak areas were measured using the Marquardt algorithm to fit a Lorenzian type. Resonance peak assignments of major neurometabolites at *in vivo* ^{1}H MRS were NAA at 2.0 ppm, Cr at 3.0 ppm, and Cho at 3.2 ppm. The quantitative expression of results was evaluated with the intensity of the Cr resonance as a reference.

4. Statistical analysis

Statistical analysis was performed using SPSS (SPSS for Windows, Version 10.0, SPSS Inc., Chicago, IL). Data were analyzed with two-tailed t test, where $P<0.05$ was considered statistically significant to account for multiple comparisons.

RESULTS

1. MRI findings

A well defined, hyperintense signal lesion is noted in the right parietal cortex on T2-WT transverse image. Adjacent focal defect of skull is seen as abrupt discontinuity of dark signal intensity. This finding indicates cortical contusion and adjacent dural injury.

2. MRS findings

For the voxel defining of normal ICR mouse brain, T1-WT transverse image is selected for localized water-suppressed *in vivo* ^{1}H MRS (Fig. 3). Because brain contusion was well demonstrated in the T2-WT MR image, T2-WT MR image is selected for localized *in vivo* ^{1}H MRS for the voxel defining of contusional brain induced by fluid percussion injury (Fig. 4). Typical spectra obtained from experimental traumatic brain contusion of ICR mouse and controls are shown in Fig. 5 and Fig. 6. As can be seen in Fig. 5 and 6, spectral patterns of the right parietal cortex between the trau-

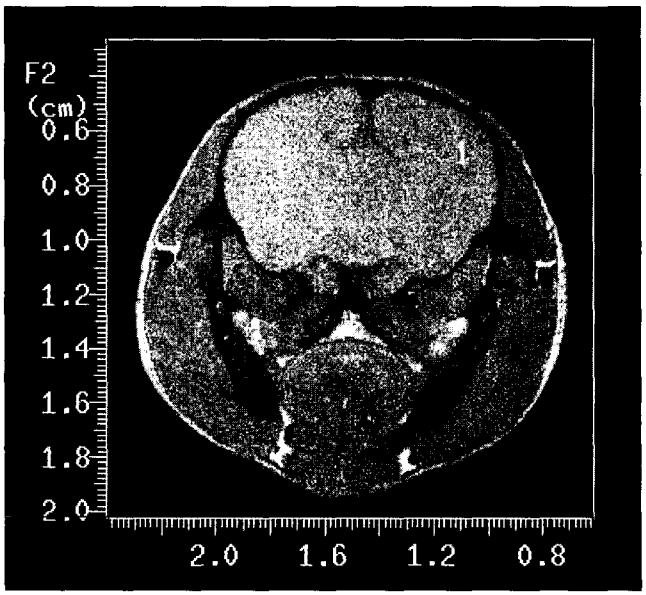

Fig. 3. T1-WT transverse MR image of a normal ICR mouse brain in the right parietal cortex covering subcortical and basal ganglia defining the voxel selected for localized water-suppressed *in vivo* ^{1}H MRS.

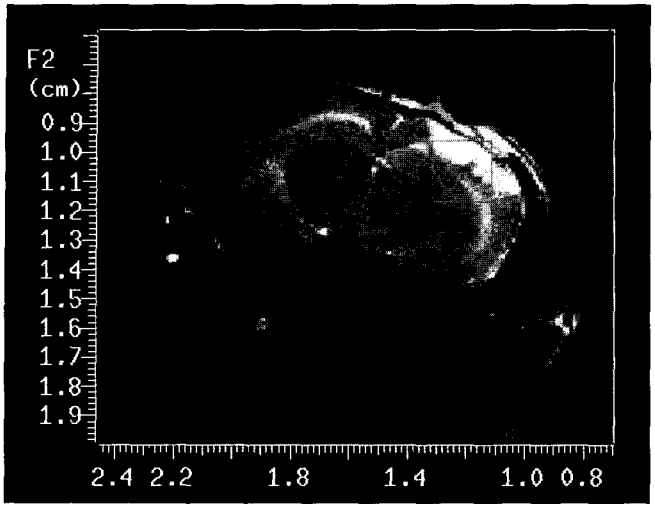

Fig. 4. T2-WT transverse MR image of traumatic contusion induced by FPI. The voxel selected for localized water-suppressed *in vivo* ^{1}H MRS was noted.

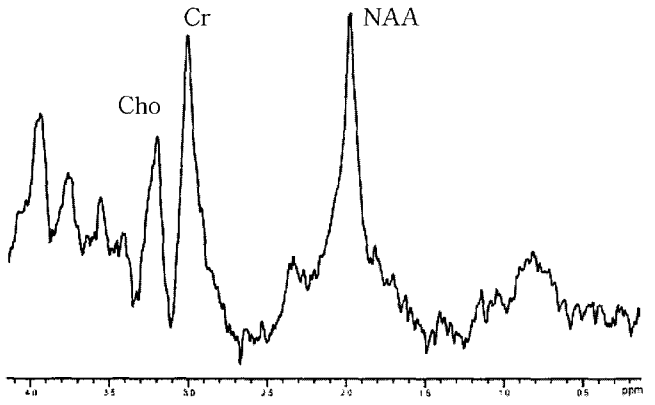

Fig. 5. Localized, water-suppressed *in vivo* ^{1}H magnetic resonance spectra obtained from the normal ICR mouse brain.

matic brain contusion and the controls are substantially different. In particular, NAA signal intensity in traumatic brain contusion induced by FPI showed a marked decrease compared with that seen in normal control.

In Table 1, the specific feature in traumatic brain contusion was a significant decrease of NAA/Cr ratio compared control subjects (P=0.001). The ratio of NAA/Cr in traumatic brain contusion was 0.90±0.11, while that in normal control subjects was 1.13±0.12. Cho/Cr ratio had a tendency to rise in experimental brain contusion (P=0.02). Cho/Cr ratio was 0.91±0.17, while that in normal control subjects was 0.76±0.15. However, no significant difference of Glx/Cr was established between

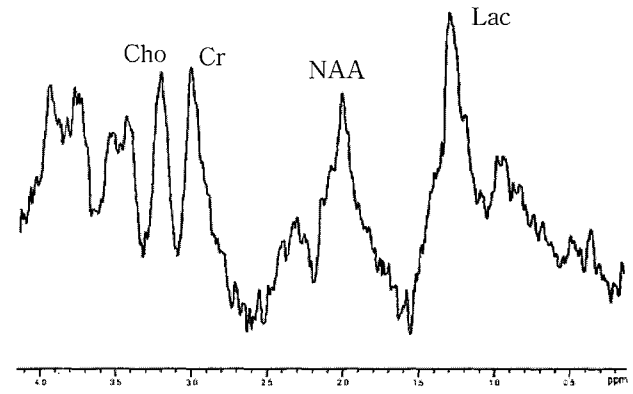

Fig. 6. *in vivo* ^{1}H magnetic resonance spectra obtained from the same ICR mouse brain after FPI. Compared to the normal brain, a marked reduction in the NAA intensity and increased Cho/Cr ratio is noted in the traumatic contusional brain.

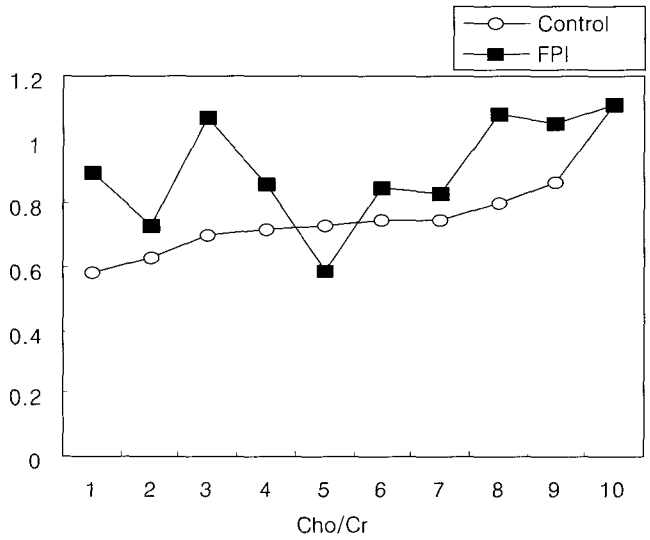

Fig. 7. Comparison of Cho/Cr ratios between normal controls and traumatic contusion of ICR mouse brain induced by FPI.

experimental traumatic brain injury models and normal controls. Fig. 7-10 show the comparisons of proton metabolite ratios (Cho/Cr, Glx/Cr, NAA/Cr) between FPI group and normal control. Lactate was detected in 6 of 10 spectra of experimental brain contusion group, while no lactate was detected in control subjects.

DISCUSSION

FPI in rats is a commonly employed and clinically relevant model of experimental concussive traumatic brain injury[7]. Recently, molecular neurobiology has ad-

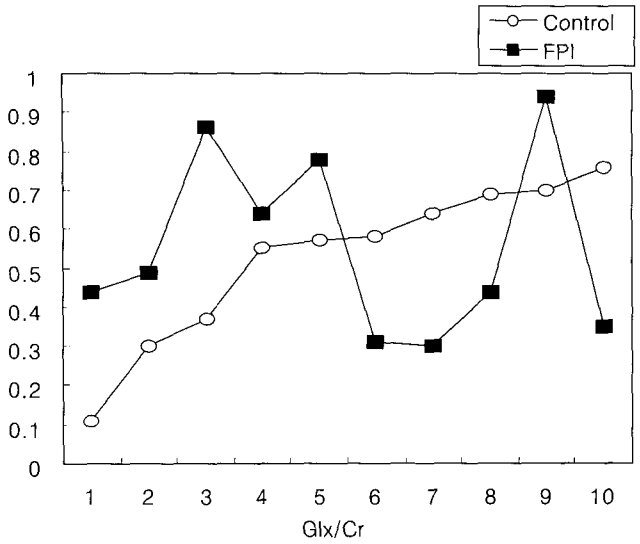

Fig. 8. Comparison of Glu/Cr ratios between normal controls and traumatic contusion of ICR mouse brain induced by FPI.

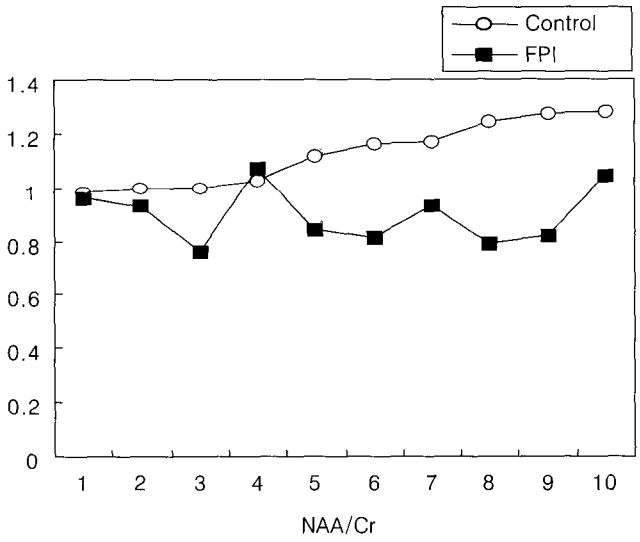

Fig. 9. Comparison of NAA/Cr ratios between normal controls and traumatic contusion of ICR mouse brain induced by FPI.

vanced through the use of genetically altered mice. These mice provide valuable insight into the molecular mechanisms of cell-cell interactions and cell metabolism through manipulation of the expression of a broad spectrum of genes. Many of these genes are important in the normal development, maintenance, and plasticity of the central nervous system. The recovery and pathophysiology of traumatic brain injury may rely on many of the same mechanisms operant in development[12]. Some of these mechanisms include axon target selection, synapse formation and remodeling, and neuronal survival. Therefore, the FPI model, when applied to these genetically altered mice, may be a particularly useful experimental tool for investigating specific neurologic, histopathologic, and behavioral sequelae of traumatic brain injury in the absence or over-expression of certain gene products-giving insight simultaneously at molecular and systemic levels[13]. Further, they may become extremely useful for studying the molecular mechanism of traumatic brain injury correlating MRI and MRS[14]. We successfully applied the FPI to the ICR mouse brain and acquired the MR imaging and MR spectrum from ICR mouse brain through using 4.7 T Varian MRI/MRS system. These results based on MR imaging and MR spectrum from ICR mouse brain would be helpful in the research field of neurologic brain damages in veterinary medicine.

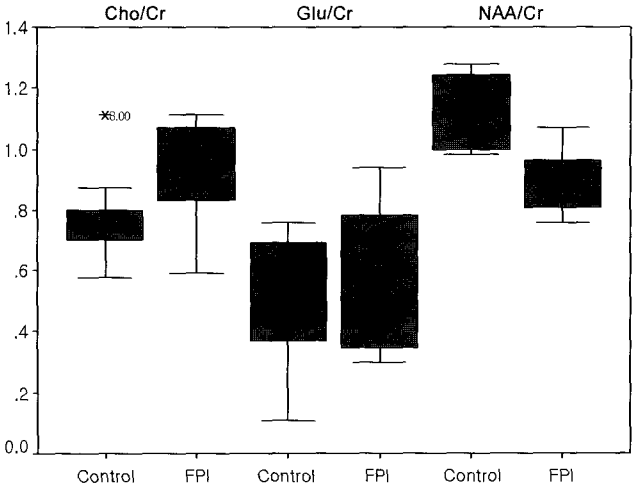

Fig. 10. MRS metabolite ratios of the contusional trauma model induced by FPI in comparison to ratios of the normal controls.

in vivo ^{1}H MRS is most sensitive to unbound, freely mobile metabolites and has clinical applications to categorize noninvasively the various states of metabolic or biochemical disorders[15]. The spatially localized, water-suppressed stimulated-echo acquisition method pulse sequence that samples the relative levels of mobile metabolites from a volume of interest defined from an MR image has provided a valuable biochemical basis for intergrading anatomic and pathologic information obtain-

ed from MRI. The present study shows that it is possible to monitor proton metabolites, including neurochemical compounds that may be involved in diazepam anesthetized normal ICR mouse brain and fluid percussion injury brain.

NAA is the dominant peak in normal adult human or animal brain spectra. It is accepted as a neuronal and axonal marker whose physiological role is currently unknown. It has been shown to increase during brain development after birth and in childhood and to decrease in old age[16]. Reduced NAA has been observed with many neurological diseases that cause neuronal and axonal degeneration: epilepsy, dementias, stroke, hypoxia, multiple sclerosis, and leudoencephalopathies[17]. This genetic disorder results in a deficit in the enzyme that breaks down NAA. Evidence has been found suggesting that the behavior of this peak may be affected by other metabolite peaks occurring at the same location. The peak at 2.0 ppm contains a small contribution from N-acetyl-aspartate-glutamate (NAAG) and other metabolites : it is sometimes referred to as the N-acetyl group peak instead of simply NAA.18

The major peak at 3.0 pm is from the CH3 group of creatine and phosphocreatine (Cr+PCr), referred to as total creatine (Cr). Another Cr+PCr peak, from the CH2 group, can be observed at 3.9 ppm if good suppression of the water peak at 4.7 ppm is achieved; however, only the peak at 3.0 ppm is typically employed in the interpretation of spectral data since it has a larger area. Total Cr has been considered to be stable enough to be used as an internal reference in reporting relative concentrations of other brain metabolites, but recent findings suggest that this assumption should be used with care. Examples of total Cr variations include an increase with trauma and a decrease with hypoxia, stroke, and tumor[19].

The peak at 3.2 ppm is a mixture of choline (Cho) and choline-containing compounds. Choline is thought of as a product of myelin breakdown. The peak is generated by the nine protons in the $(CH_3)_3$ group of the choline molecule and contains information related to cell density. Choline is the dominant peak in long TE spectra of normal neonate brain. In adult brain, an increase in the Cho peak area is associated with Alzheimer's disease, chronic hypoxia, post liver transplant, and epilepsy, while a decrease is seen in hepatic encephalopathy. Malignant glial tumors and a variety of primary brain tumors also show evaluated Cho resonance. Several questions remain to be answered regarding the choline peak composition and its variation with metabolic processes[20].

Lactate, when present, appears at 1.33 ppm as an inverted doublet with PRESS and a TE=135 ms. The doublet is upright with PRESS at TE=270 ms and with STEAM at any TE. Having a concentration of about 1 mM, lactate is not usually seen in the spectra of normal brain. Lactate has been detected in patients with stroke, some brain tumors, hypoxia, anoxia, and mitochondrial encephalopathies[21]. It has been observed to increase in the epileptic focus immediately following a seizure. Lactate production has been measured with ^{1}H MRS during the early stage of focal brain activation. With physiological photic stimulation a transient increase was reported in lactate levels of the visual cortex[22].

Other signals seen on short TE include glutamine (Gln) and glutamate (Glu), GABA, and commonly referred to as Glx peaks. Protons of the β-CH_2 and γ-CH_2 groups of Glx produce peaks in the 2.0-2.5 ppm range. These are very small peaks due to complex coupling processes and fast T2 decay. They are hardly seen in normal brain spectra but become more visible as a result of elevated glutamine in brain injury or some encephalopathies. The Glx peaks increase in cases of near drowning, hypoxia, and hepatic and hypoxic encephalopathies[23]. Gamma-aminobutyric acid (GABA) has peaks at 1.9 and 2.3 ppm from protons in the α- and β-CH_2 groups, and at 3.0 ppm from the γ-CH_2 group. This latter peak is usually hidden by the Cr+PCr peak that occurs at the same location but may be detected using spectral editing techniques that remove the Cr peak. The GABA concentration has been shown to increase with the administration of vigabatrin, an antiepileptic medication[24]. Suggestions have been made to use GABA for monitoring patients with epilepsy that

are being treated with vigabatrin.

Mobile lipid signals resulting from pathology appear as sharp peaks at 0.9 and 1.3 ppm and interfere with lactate when it is also present. Lipid signals are more prominent with short TE sequences. They are seen in some tumors, stroke, and acute MS lesions, and appear to be associated with acute destruction of myelin[25].

In veterinary medicine, animals usually need general anesthesia during the MRI and MRS data collection. For human studies, children and other uncooperative patients often need sedation or general anesthesia during the MRS examination[26]. The administration of lorazepam to manage agitation or anxiety in individual cases who require a sedative for successful completion of 1H MRS studies can be performed, as doing so does not change significantly the main chemical measures that are part of the *in vivo* human ^{1}H MRS brain spectra. These findings have important implications for *in vivo* MRI and MRS studies in neuropsychiatric populations, and demonstrate the feasibility of approaches that would require sedation of patients with benzodiazepinic agents. In our study, diazepam and xylazine anesthesia does not interfere with the main MRS-visible brain metabolites. But, it is necessary to investigate in detail the effect of various agents for anesthesia on MR spectroscopic results.

In the region of the contused parietal cortex covering the subcortical white matter, we observed significant metabolite changes compared to normal cortex. The decrease of NAA might indicate neuronal cell loss. It is considered as markers of neuronal integrity. NAA is unequivocally specific to neurons and a decrease of NAA in MRS has been shown to be equivalent to neuronal loss. In humans after traumatic brain injury a decrease of NAA correlated positively to adverse outcome and neuropsychologic dysfunction[27]. Choline and Inositol have been reported elevated following days to weeks after human trauma either as a sign of membrane breakdown/synthesis or inflammation[28]. In rats the inflammatory activity is known to reach a maximum on 4-6 days after experimental brain contusion and to persist for months. In our study, the increase of Cho/Cr at 3 days might therefore be an indicator of increased inflammatory reactions. Lactate was detected in 6 of 10 spectra of FPI models. The increased rate of lactate detection on the injured cortex covering subcortical white matter area indicates a post-traumatic shift of energy metabolism towards anaerobic glycolysis. At a post-acute time after 24 hours when hypoperfusion and ischemia in this model should have resolved there is still high lactate suggesting persistent hyperglycolysis[29].

In the present study, we applied ^{1}H MRS in a normal controlled setting to a mouse contusional trauma model. In individual cases however, the disturbed magnetic field homogeneity caused by an intracontusional hemorrhage and containing skull area in voxel can potentially prevent acquisition of useful spectra. To increase the clinical usefulness of the method, future research has to link the observed metabolite changes to known post-traumatic mechanisms. Whereas a single voxel MRS technique provided direct metabolic information from the volume of interest in MR images, MR spectroscopic imaging currently in use would provide maps of metabolites throughout the brain in comparable study times. Although MR spectroscopic imaging needs to be improved to prevent signal contamination of adjacent grids, the improved MR spectroscopic imaging technique would be a good candidate to study the integrity of glial cell membranes in cortex, subcotical white matter and white matter fiber tracts due to altered diffusion anisotropy in FPI. Furthermore the exact quantification of metabolites instead of semiquantitative ratios versus creatine, which might not be as stable in this model as generally supposed, will improve results.

In conclusion, we successfully applied noninvasive, image-guided, localized, water-suppressed *in vivo* 1H MRS to the traumatic contusion of ICR mouse brain induced by FPI. Significant MR spectral differences were observed between FPI and normal controls. These findings strongly suggest that *in vivo* 1H MRS may be a useful modality for clinical evaluation of traumatic contusion and could aid in better understanding the neuropathologic process of traumatic contusion in-

duced by FPI. It is necessary to investigate the spectral alterations in various degrees of FPI for the further detailed analysis.

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유체타진손상기법에 의한 ICR 쥐의 뇌손상 : 자기공명분광법

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실험적 뇌손상 전후에 쥐의 뇌대사물질 변화를 4.7 T 자기공명분광법을 이용하여 조사하여 보았다. 자기공명 스펙트럼는 비교대상 그룹으로서 정상 쥐 우측 두전엽 피질에서 획득되었다. 유체타진손상기법(Fluid Percussion Injury)을 사용하여 뇌손상을 유발시킨후 3일 후 스펙트럼이 얻어졌다. 뇌손상 쥐의 뇌대사물질들의 변화는 정상쥐의 뇌대사물질들과 비교되었다. Neuronal marker로써 NAA/Cr 비율은 대조군에서 1.13±0.12이었고 뇌좌상부위에서 0.90±0.11로 손상전과 비교하여 대조군에 비해 유의성있는 감소소견을 나타내었으며 이는 neuronal loss를 의미하는 것으로 추정된다(P=0.001). Cho/Cr 비율은 대조군에서 0.76±0.15이었고 뇌좌상부위에서 0.91±0.17로 손상전과 비교하여 대조군에 비해 유의성있게 증가하는 경향을 나타내었으며 이는 생체막의 파괴나 염증반응과 관련된 것으로 추정된다(P=0.02). 하지만 Glx/Cr 비율은 손상전후에 유의성있는 변화를 나타내지 않았다. Lac/Cr 비율은 대조군에 비해 증가하는 경향을 나타내었고 이는 외상후 에너지 대사의 변위양상으로 고려되어진다. 이러한 소견들은 자기공명분광법이 유체타진손상기법을 이용한 외상성 뇌좌상에서 신경병리학적 변화과정에 대한 이해를 증진시키고 나아가 외상에 의한 뇌좌상의 임상적인 평가를 위해 매우 유용한 modality임을 시사하는 것이라고 사료된다. 그러나 본 연구에서 몇몇의 케이스에서 voxel을 선정하면서 두개골의 일부가 포함되거나 혹은 좌상과 동반된 출혈로 인해 유용한 데이터를 획득하는데 어려움을 주기도 하였다. 앞으로 보다 더 세밀한 분석과 연구를 위해 유체타진 손상의 다양한 정도에서 대사물질들의 변화양상을 평가할 필요가 있을 것으로 사료된다.

중심단어 : 자기공명분광법, 뇌손상, 유체타진손상기법