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Clinical and Experimental Applications of ^{1}H MRS

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Image-guided localized, water-suppressed in vivo ^{1}H MR spectroscopic studies were performed on the patients with brain tumors, acute cerebral infarction and schizophrenia, and dogs. GE Signa 1.5 T whole-body MRI/MRS system using STEAM pulse sequence was used. Proton metabolite ratios relative to creatine (Cr) were obtained using a Marquart algorithm. In vivo ^{1}H MR spectra in brain neoplastic tissues revealed the changes of signal intensities of N-acetylaspartate (NAA), choline (Cho) and lactate (Lac) resonances. The present results suggest that the observed metabolite alterations from localized, water-suppressed in vivo ^{1}H MR spectroscopy can be useful as an index of brain tumors, cerebral infarction and schizophrenia, and provide good quality metabolic information of cerebral tissue in the field of thanato-chronology.

INTRODUCTION

Over the past few years, in vivo ^{1}H MR spectroscopy (MRS) has been successfully employed in living systems to identify and quantify the levels of biochemical compounds, and to investigate the metabolism and biochemistry of a variety of diseases and disorders. Improvements in localization, water-suppression techniques, and instrumentation for MRS and the relatively high MR sensitivity have led to a wide range of clinical applications to the non-invasive studies of various human tissue such as brain, muscle, bone without the need for radioactive isotope administration[1]. Protons were initially selected because of the highest natural abundance, the high relative receptivity, the commonest in the biological systems, and the determination of the three-dimensional macromolecular structures on the basis of nuclear Overhauser effect. In most of ^{1}H MRS studies, MRS was used to investigate the aspects of cellular processes in isolation or the influences of different processes in isolation on the resonance of water in intact cells. In vivo ^{1}H MRS studies are handicapped, however, by the large number of metabolites which give many overlapping peaks and produce the very complex spectra. Coupling between the spins of particular protons causes resonances to occur as doublets, triplets, or more complicated multiplets. The application of ^{1}H MRS to the study of living tissue has in the past been hindered by the technical problems posed by the presence of 110 molar concentration of the protons of water as a background signal. The relative size of this signal can now be reduced substantially by a variety of water

suppression schemes, such as PRESS and STEAM pulse sequences. A large number of proton-containing metabolites can be detected when these pulse sequences are employed. The recent development of spatial localization methods, which sample the relative levels of mobile metabolites from a volume of tissue defined from an MR image, has provided a basis for integrating the biochemical and pathological information obtained from MRI. This combination of metabolic and anatomic information offers a new means for understanding the origins and the time course of progression in a variety of diseases. Although any nucleus possessed a nuclear spin can give rise to an MRS absorption signal, the initial chemical and biological MRS studies focused on proton spectra exclusively. Recently, in vivo ^{1}H MRS has been applied to measure proton metabolites such as N-acetylaspartate (NAA), creatine/phosphocreatine (Cr), choline-containing compounds (Cho), myoinositol (Ins), lactate (Lac) and neurotransmitters, g-aminobutyric acid (GABA), glutamate (Glu) and glycine (Gly).

Localized, water suppressed in vivo ^{1}H MRS enables investigation of specific metabolites within brain tissue and provides the biochemical metabolic information that cannot be obtained by any other modalities in the brain. Thus, in vivo ^{1}H MRS is the unique technique in clinical medicine that provides noninvasive access to living samples[1]. The biochemical metabolic information of normal and neoplastic tissue by MRS can supplement anatomical and morphological information provided by magnetic resonance imaging (MRI). For the diagnosis of the human brain tumors the combination of MRI and MRS has developed to a stage that enables routine study in a clinical environment[2].

MATERIALS and METHODS

All localized, water-suppressed in vivo ^{1}H MRS studies were performed on 1.5 T MRI/MRS system (GE Signa Advantage, version 4.8 ; GE Medical System, Milwaukee, Wisconsin) using a stimulated echo acquisition mode (STEAM) pulse sequence[3-5]. As a single voxel technique, a 2x2x2 cm^3 (8 ml) or 1.5x1.5×1.5 cm^3 (3.375 ml) voxel was selected using the T1-weighted MR images (20 ms TE, 400 ms TR).

Spectral parameters were: 20 ms TE, 2000 ms TR, 128 averages, 2500 Hz spectral width, 2048 data points. The total examination time per case was approximately 40 minutes. All of the in vivo ^{1}H MR spectra were acquired with use of the standard bird-cage quadrature head coil (GE Medical Systems, Milwaukee, Wisconsin) that produces a uniform RF field (63.86 MHz). Raw data were transferred to a Sun SPARC station IPC (Sun Microsystems, Mountain View, California) and processed by the SAGE data analysis package (GE Medical Systems, Milwaukee, Wisconsin).

The shimming procedure focused on the water signal was performed to obtain the uniform and homogeneous magnetic field. Typical water line width (full width at half maximum) was 3−4 Hz. Special attention was given to locating the water signal frequency to maximize the water suppression. An exponential line broadening of 0.5 Hz was applied. Time domain

data were converted to frequency domain by Fourier transformation. Frequency domain spectra were phased by hand, with use of frequency-independent phase corrections only. Phased absorption spectra are reported directly without baseline correction or resolution enhancement. All of the ^1H MR spectra were plotted and blindly analyzed in the absorption mode, and fitted to Lorentzian lineshapes. Peak areas for each proton metabolite were measured using a Marquardt algorithm[6]. Proton resonances in the spectra obtained from brain tissues were assigned on the basis of prior assignments[7]. Resonance peak assignments of major ^1H MRS observable metabolites were CH_3 of NAA, 2.00 ppm ; $N-CH_3$ of Cr, 3.00 ppm ; $N-(CH_3)_3$ of Cho, 3.20 ppm ; $-CH_2$ of Glu, 2.35 ppm ; $-CH_2$ of GABA, 2.25 ppm ; H4 and H6 of Ins, 3.50 ppm. It is very complicated to resolve GABA and Glu at 1.5 T in vivo, although the chemical shifts of $-CH_2$ groups of GABA and Glu were assigned as 2.25 and 2.35 ppm, or 2.30 and 2.35 ppm, respectively. Both $-CH_2$ groups of GABA and Glu are a triplet around 2.3 ppm. Since $-CH_2$ groups of GABA and Glu were not convincingly resolved in the region from 2.25−2.35 ppm, they were approximated with two single peaks at 2.25 and 2.35 ppm, respectively. Then, it was achieved to combine GABA and Glu into a single measure GABA+Glu. Only $-CH_2$ groups of GABA and Glu were particularly conside red because $-CH_3$ and $-CH_2$ groups were severely overlapped with the other major metaboli tes[8]. To obtain the relative metabolite ratios, Cr was used as a putative reference[9].

Statistical analysis was performed using SPSS (SPSS for Windows, Version 6.0, SPSS Inc., Chicago, Illinois). The data were analyzed with paired-samples t tests, where $p<0.05$ was considered significant to account for multiple comparisons. In particular, Pearson product-moment (bivariate) correlation analysis was performed between BPRS changes and the changes of metabolic ratios, where $r>0.7$ was considered correlative.

Clinical Application

Brain Tumors

^1H MRS readily distinguishes normal brain tissues from astocytomas. However, ^1H MRS may not be able to distinguish between different histologic grades of malignancy in astrocytomas. Some investigators have proposed that the presence of lactate correlates with a higher degree of malignancy and that it is commonly observed in glioblastoma multiforme. The typical ^1H MR spectroscopic characteristics of astrocytomas include a significant reduction in NAA, a moderate reduction in Cr, and an elevation of Cho. Reduction of Cr is probably related to an altered metabolism, and elevation of Cho may reflect increased membrane synthesis and cellularity. Elevation of lactate may reflect tumor hypoxia. The Cho peak also is increased in the more-malignant astrocytomas. ^1H MRS may be used to distinguish infection from a tumor, because the former has extremely low concentrations of Cho. ^1H MRS may also play a role in monitoring the response of astrocytomas to treatment. In some instances, ^1H MRS may detect tumor recurrence before MR images become abnormal.

Fig. 1 shows the T1-weighted axial MR image of brain tumor as glioblastoma multiform

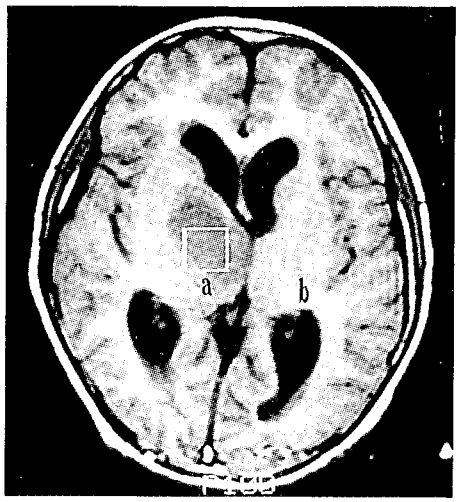

Figure 1. T1-weighted axial MR image of glioblastoma multiform in right thalamus. The voxel (a) contains the malignant tissue of glioblastoma multiform and the voxel (b) contains the potentially normal tissue.

of the right thalamus indicated by the right voxel for localized in vivo ^{1}H MRS. The voxel (a) contains the malignant tissue of brain tumor and the voxel (b) contains the potentially normal tissues. Fig. 2 shows a water-suppressed in vivo ^{1}H MR spectra obtained from the

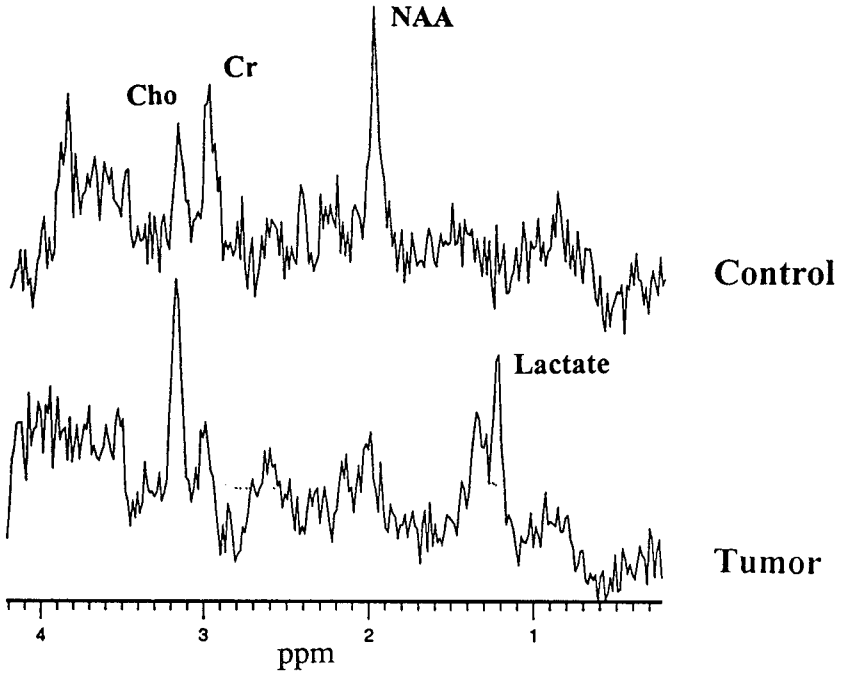

Figure 2. Localized, water-suppressed in vivo ^{1}H MR spectrum obtained from the voxel (a) glioblastoma multiform. NAA has the lowest signal intensity while Cho has the highest signal intensity. Lactate signal at 1.3 ppm is highly elevated, compared with the normal tissue.

malignant tissue of the voxel (a) and the potentially normal tissue of the voxel (b), respectively. In Fig. 2, in vivo ^{1}H MR spectrum from the glioblastoma multiform is very different from that of normal brain tissues. The specific features of spectrum from the glioblastoma multiform reveal a decrease of the NAA and Cr signal intensities and an increase of the Cho signal intensity relative to potentially normal brain spectra. The connecting line of the highest peaks of NAA, Cr and Cho has a positive slope in normal tissues, and a negative slope in malignant tissue of glioblastoma multiform. The Cho resonance from the glioblastoma multiform has the strongest intensity in the proton metabolites while the NAA resonance has the weakest signal intensity. A lactate signal has been detected in all tumor spectra. The assignment of lactate is based upon its chemical shift (1.30 ppm) and its coupling constant (about 7 Hz)[10]

Cerebral Infarction

Because early and aggressive treatment (including intraarterial thrombolysis performed by radiologists) of cerebral infarctions is being currently evaluated, a noninvasive diagnostic test that confirms the presence of hyperacute strokes is desirable. CT changes are difficult to identify during the first 24 hours after the ictus. Although MRI abnormalities may be present as early as 3 hours after the onset of symptoms, permanent tissue damage may be already present at that time. In humans, ^{1}H MRS performed in the initial 24 hours after a stroke shows elevation of lactate implying ischemia. Decreased NAA may be observed as early as 4 days after infarction. Chronic infarctions show decreased NAA, Cr, and Cho, but no evidence of lactate. Experimentally, an increase in lactate may be detected after only 2 to 3 minutes of cerebral ischemia. In these animals, the lactate returned to normal when the hypoxic insult was reversed. The role of ^{1}H MRS in the evaluation of human hyperacute cerebral infarction still needs to be evaluated. White matter hyperintensities on T2-weighted MR images are common and are found in approximately 30% of patients older than 60 years age. Their cause is uncertain but differentiating them from true infarctions is important. ^{1}H MRS shows that these age-related white matter changes contain normal levels of NAA and Cr. Their Cho level is increased, suggesting an alteration of the white matter phospholipids. Systemic disorder, which result in central nervous system vascularitis, may be subclinical for prolonged periods of time. Patients with lupus erythematosus have decreased NAA/Cr ratios. These ratios are lower in patients with concomitant severe cerebral atrophy and probably reflect neuronal loss.

In all infarct patients, the T2-weighted MR images clearly showed the infarcted region as hyperintense signal. The spectral characteristics in the infarcted regions were a decrease of NAA/Cr ratio and an appearance of Lac signal, compared with the control region. NAA/Cr ratio was generally decreased by approximately 20 %. Significantly elevated Lac level was observed in all infarcted regions, while no Lac was found in the control regions. The other metabolite ratios such as Cho/Cr and Ins/Cr were not correlated in the infarcted and control regions.

Figure 3 shows a conventional T2-weighted axial MR image which depicts a well-defined high signal intensity lesion representing infarction in the left hemisphere. The localized voxels corresponding to $2\times2\times2$ m^3 for ^{1}H MRS measurement was shown in Figure 3. Spectral pattern of the infarcted region was substantially different from that of contralateral region in Figure 4. Doublet of high intense Lac signal assigned at 1.26 and 1.36 ppm was observed

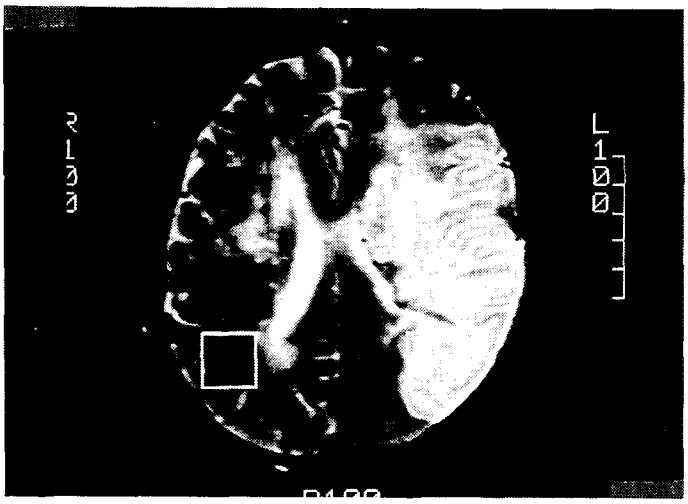

Figure 3. T2-weighted axial MR image of acute infarction in MCA defining voxel A of the infarcted region and voxel B of the control region.

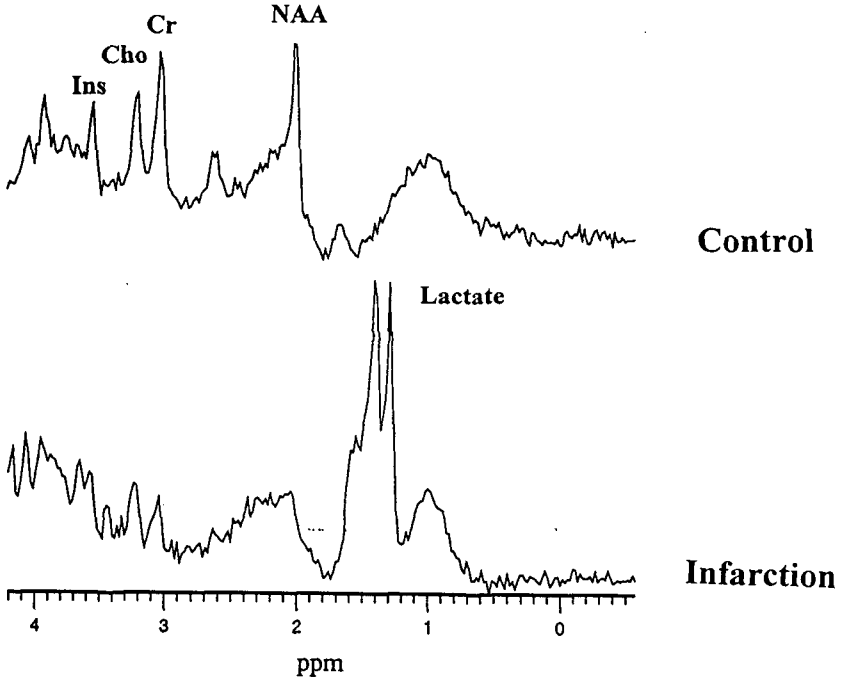

Figure 4. Localized, water-suppressed in vivo ^{1}H MR spectra obtained from the infarcted region (A) and control region (B). Chemical shifts are indicated in parts per million (ppm).

in infarcted region.

Schizophrenia

Figure 5 shows the T1-weighted axial MR image of chronic schizophrenia subjects with the right and left prefrontal voxels selected for localized in vivo ^{1}H MRS. Typical spectra

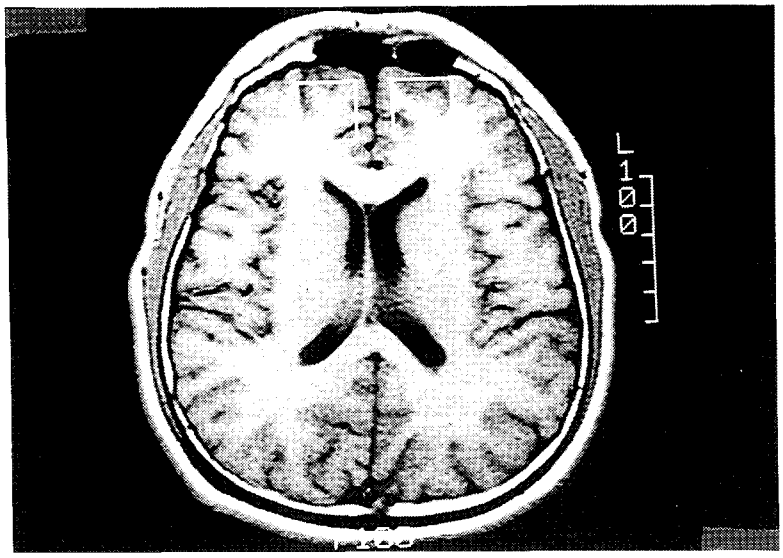

Figure 5. T1-weighted axial MR image of chronic schizophrenia with the right and left prefrontal voxels selected for localized in vivo ^{1}H MRS.

obtained from the right and left prefrontal voxels in schizophrenia are shown in Figure 6. No significant lateral effect was established for any metabolic ratio in patients and controls ($p>0.05$). Chronic schizophrenic patients had a significantly higher (GABA+Glu)/Cr ratio ($p=0.005$) and lower NAA/Cr ratio ($p=0.023$) than did control subjects.

The spectral characteristic in schizophrenia after neuroleptic treatment generally demonstrated a decrease of the complex of GABA and Glu signal intensities, compared with that before neuroleptic treatment. Decreased (GABA+Glu)/Cr ratio was observed in 29 patients among 34 follow-up patients, indicating metabolic improvement. Among 29 metabolically improved patients, five, nine, fifteen patients were assigned markedly, moderately, slightly improved, respectively. Only 5 patients shows slightly increased (GABA+Glu)/Cr ratio, indicating slightly metabolic deterioration. Thus, MRS showed that 29 patients got better and 5 patients got worse metabolically. Since BPRS decreased in all cases, all chronic schizophrenic patients clinically improved after neuroleptic treatment. Hence, the present follow-up result shows a significant correlation ($r=0.76$) with BPRS on the basis of (GABA+Glu)/Cr ratio. After neuroleptic treatment, there were no significant changes in the other proton metabolite ratios such as Cho/Cr, Ins/Cr. In case of NAA/Cr ratio, it increased in the 13

patients among 34 follow-up patients.

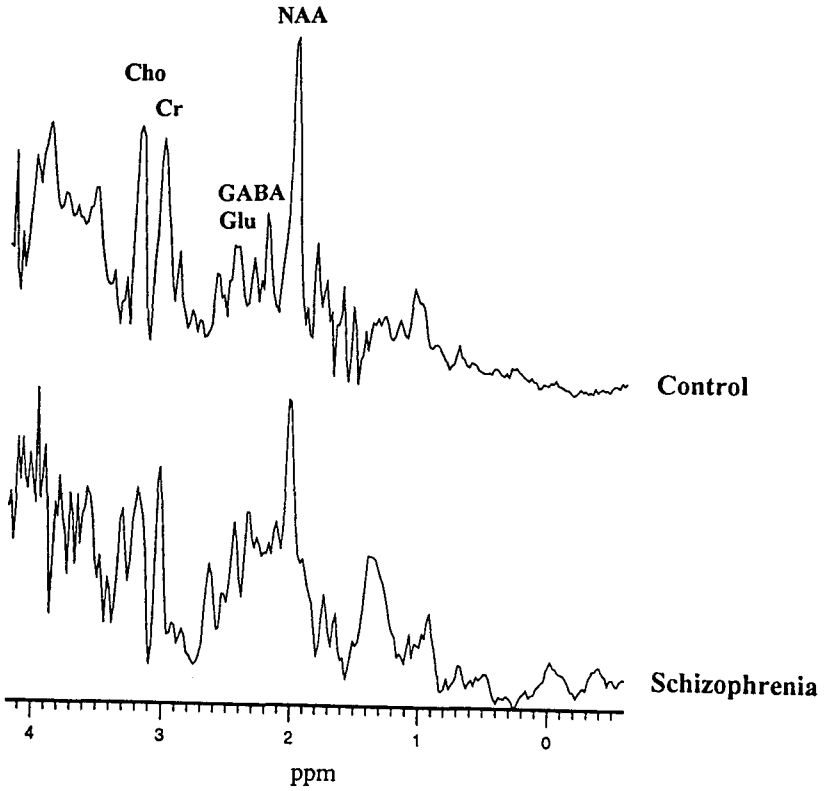

Figure 6. Typical in vivo ^{1}H MR spectra obtained from the right and left prefrontal voxels in schizophrenia. Chemical shifts are indicated in parts per million (ppm).

Experimental Application

Dog Brain

The volume of interest (VOI) included tissue outside the thalamus of the dog (Figure 7). All of the proton metabolites were identified in the ^{1}H MR spectrum of the premortem and postmortem period. In the premortem period the proton metabolite components of brain tissue predominantly consist of NAA, Cr, Cho, and Ins. Spectral intensities of metabolites were substantially changed with respect to postmortem time lapse. The 30 minutes postmor tem spectrum was characterized by the appearance of the Lac resonance signal. The resona nce signal of Ins was distinctly increased in the 24 hours postmortem period. At 48 hours, the postmortem spectrum revealed decomposition of proton metabolites, particularly NAA and Lac.

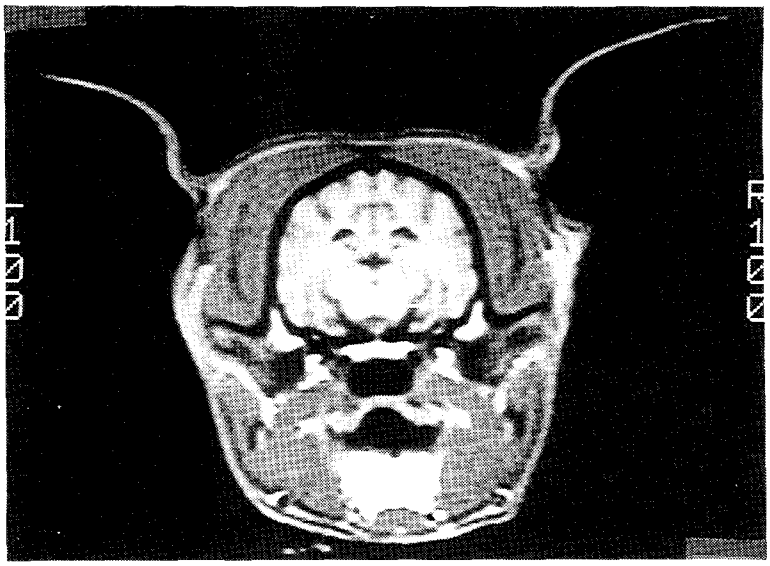

Figure 7. T1-weighted axial MR image of the dog brain defining the volume of interest (VOI) selected for localized in vivo ^{1}H MRS.

Figure 8 shows the alterations of proton metabolite ratios in the thalamus from the premortem and the early postmortem period. Lac/Cr ($p=0.015$) and Ins/Cr ($p=0.027$) ratios were significantly changed in the postmortem time period. Lac/Cr and Ins/Cr ratios generally increased from 30 minutes to 180 minutes postmortem. By 24 hours postmortem, Lac/Cr ratio decreased somewhat while the Ins/Cr ratio continued to increase. However, NAA/Cr ($p=0.12$) and Cho/Cr ($p=0.08$) ratios were generally unchanged in the early postmortem period.

DISCUSSION

The capability of a non-invasive method, graphically localized, water-suppressed in vivo ^{1}H MRS has been demonstrated to monitor metabolic levels of brain tumor tissue in patients. Our preliminary studies show that all in vivo ^{1}H MR spectral patterns of tumors differed from those of normal brain tissues. It is easy to identify the condition of tissues because of the different pattern of spectrum between the normal and tumor tissues. As the ratios of Cr/Cho, NAA/Cho and NAA/Cr in tumor spectra were significantly different from normal control spectra, the ratios of Cr/Cho, NAA/Cho and NAA/Cr in normal cerebral white matter are 1.1, 2.2 and 1.9, while those values from the glioblastoma multiform are 0.52, 0.44 and 0.85, respectively. Since the signal intensities of NAA and Cho in the proton metabolites are sensitively responded as the condition of tissue, the ratio of NAA/Cho from the glioblastoma multiform is substantially decreased four times comparing with normal tissue of cerebral

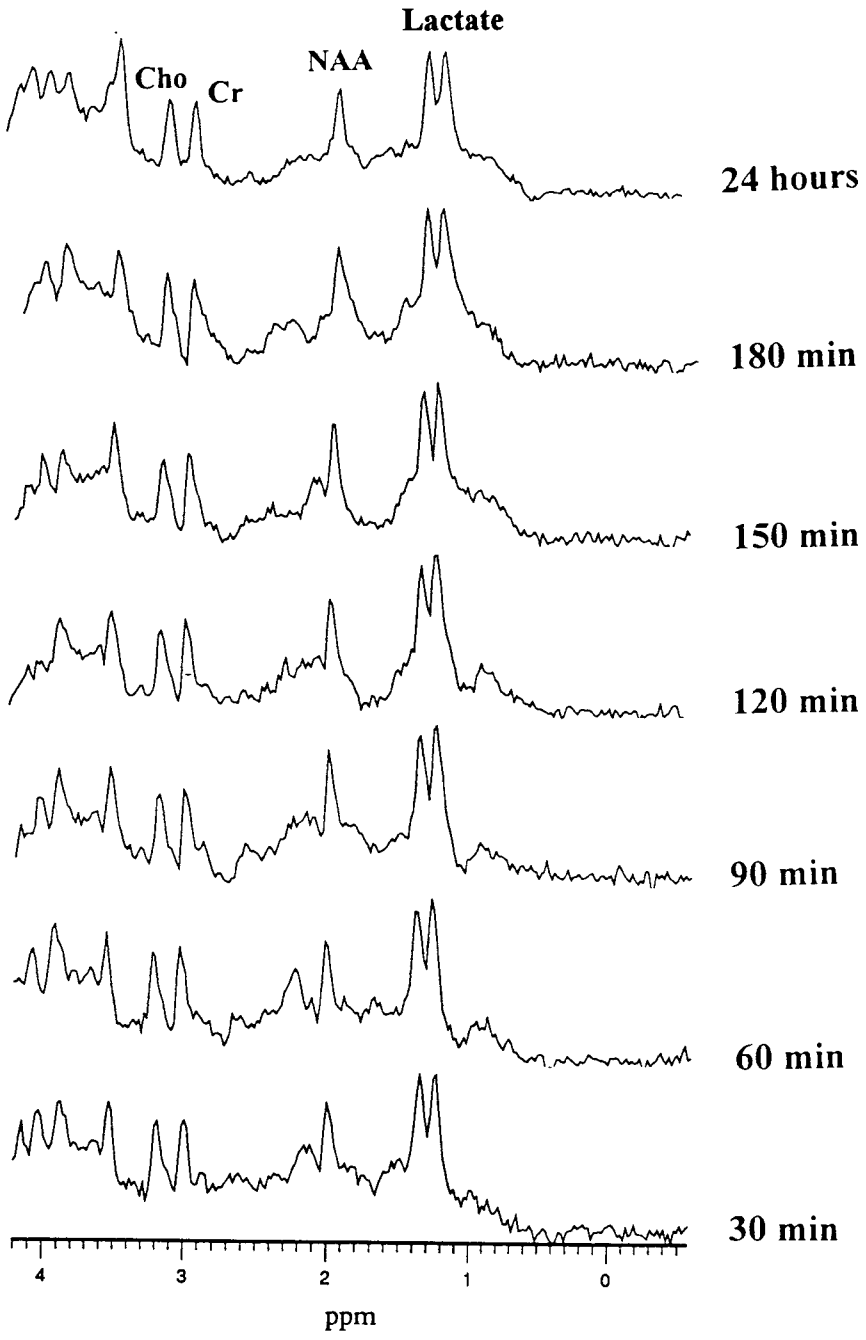

Figure 8. In vivo ^{1}H MR spectra showing the intensity changes of proton metabolites of the left thalamus of dog brain from the premortem and postmortem period. Chemical shifts are indicated in parts per million (ppm).

white matter of the right parietal lobe.

According to Kugel et al. (1992) based on the complete statistical evaluation of total 10 glioblastoma patients, the glioblastoma spectrum shown in Fig. 2 and major metabolite ratios of glioblastoma multiform in our study correspond to the level of Group I in their study[2]. It is in good agreement with Kugel et al. (1992) that the major metabolite ratios of glioblastoma multiform called glioma grade 4 have the similar values of glioma grade 2[2]. It is strikingly illustrated that the numbering system of relative ratios of proton metabolites in tumor tissue directly relates with the diagnosis of the malignant scale. Since in vivo ^{1}H MRS provides the precise numbering ratios for diagnosis of tumor grade, the final interpretation for tumor scale can be simple and convenient. Moreover, the numbering system suggests that the possibility of subjective mis-interpretation may be minimized and eventually excluded as the further development of MRS technology.

The predominant signal at 2.02 ppm in potentially normal brain tissue is that of the CH3 resonance of NAA. This compound is located almost exclusively in neurons, and believed to be a neuronal marker for the presence of intact neurons[11]. The decrease of NAA concentration in tumor tissue indicates the neuronal loss or degeneration itself, and a decrease or displacement of neurons by the tumor. An accumulation of lactate usually signifies a disturbance of normal energy metabolism due to incomplete oxidation of pyruvate[12]. The compound of lactate is believed to be an indicator of increased glycolysis [13]. The ratio of lactate/Cho in glioblastoma multiform in our study was 1.33, while that value by Kugel et al. (1992) was 0.11−0.85. This seems that the patient in our case is in the more serious condition of glioblastoma multiform since a high concentration of lactate typically corresponds to a less favorable outcome.

Cerebral infarction is associated with a marked decrease of cellular density in the region of the infarct, which largely accounts for the reduced metabolite concentrations[14]. The major findings of this study were that the pattern of metabolite reduction was uneven, the concentrations of proton metabolites such as NAA, Cr and Cho were reduced in the infarcted regions, and the Lac level was correlated with the clinical severity. The observation that proton metabolite ratios were reduced was consistent with reduced cellularity due to tissue necrosis. Our results of NAA/Cr reduction and Lac elevation in patients with infarction were consistent with those reported by Duijn and coworkers[15].

The presence of persistent Lac indicates the occurrence of increased glycolysis, which might be a marker for ongoing ischemia or other pathophysiological processes. Lac would be the best indicator of strokes in the proton metabolites presented. The importance of the relationship of Lac and pH has been examined with combined 31P and ^{1}H MRS studies[16-18]. There appears to be a Lac threshold for increasing cerebral injury as indicated by the observation of a marked decrease in intracellular pH as brain Lac exceeds 17 mol/g.

Although careful MRI studies revealed higher global rates of abnormal morphology in the frontal lobe[19-20], there are often no apparent morphologic differences in chronic schizophrenic and control subjects from MR images (Figure 5). Since a significant metabolic

difference between chronic schizophrenia and normal control was demonstrated[21], MRS may be a more sensitive modality than MRI in monitoring the progressional alterations of the schizophrenic state after neuroleptic treatment. The present study shows that the calculated proton metabolite ratios, Ins/Cr, Cho/Cr, (GABA+Glu)/Cr, and NAA/Cr, in the right and the left hemispheres of the prefrontal lobes in schizophrenia do not support a laterality hypothesis of relative hemisphere overactivation in this disorder, and that the proton metabolite ratios after drug-treated state in chronic schizophrenia were substantially altered, compared with those before drug-free state.

Although approximation of a single measure of (GABA+Glu) is more conservative in the quantification of severely overlapping peak, it has some distinct drawbacks. First, since a single measure can not reveal the specific identification of GABA or Glu in the metabolic alterations, it is uncertain which compound would really change after neuroleptic treatment. It could be GABA or Glu or both. Second, in addition to GABA and Glu, a single measure may contain other amino acids such as glutamine (Gln) because chemical shift of γ-CH2 groups of Gln is 2.45 ppm. Third, two single peaks at 2.25 and 2.35 ppm could drift since the chemical shift difference 0.1−0.2 ppm is quite sensitive to temperature variations. In the condition of unstable temperature, spectra could not provide the reliable quantitative data. Fourth, since these two neurotransmitters are counteractive each other, it could be on the horns of a dilemma to interpret alterations of a single measure in terms of neurochemical aspects.

Chronic schizophrenic patients had a significantly higher (GABA+Glu)/Cr ratio ($p=0.005$) than did normal control subjects. The increase of the (GABA+Glu)/Cr ratio in chronic schizophrenia may be indicative of abnormal neuronal function in neurotransmitters. After neuroleptic treatment, all schizophrenic subjects showed the decreased BPRS, indicating clinical improvement. The ratios of (GABA+Glu)/Cr of drug-treated schizophrenia were generally changed toward those of normal controls, indicating metabolic improvement. The decrease of (GABA+Glu)/Cr ratio was significantly correlated with the decrease of BPRS scores, indicating that the GABA and Glu concentrations are possibly associated with neuroleptic treatment. However, the other proton metabolite ratios did not show any correlation with BPRS. The reduction of GABA and Glu in drug-treated schizophrenia is implicated in balancing of the glutamate mediated neuronal excitation and recovering of neuropsychiatric disorders, and returning of normal metabolic process in the mechanism for subcortical dopaminergic hyperactivity with prefrontal deafferentation. Since clinical symptoms may be related to the concentration of GABA+Glu, the (GABA+Glu)/Cr ratio may be a valuable criterion for evaluation of response to neuroleptic treatment. Thus, our present results support the hypofrontality hypothesis of schizophrenia in terms of neurochemical aspects although this study has a regional limitation to investigate the prefrontal lobe only.

Between the premortem and postmortem period, the metabolite ratio, such as Lac/Cr was significantly changed as shown in Figure 8. The Lac resonance signal appeared immediately following death and represented tissue at risk of death (due to ischemia). The first

3 hours postmortem processes were the most active period for changes in Lac. Since Lac originates from anaerobic glycolysis, Lac concentration has reached a plateau during the 30−60 postmortem period. Postmortem Lac acidosis was well correlated with mitochondrial damage. Lac/Cr ratio then decreased to the level found at the 24 hours postmortem period. This result suggests that the Lac/Cr ratio is probably not an indication of death. Cho/Cr, NAA/Cr and Ins/Cr ratios were generally unchanged during the 180 minutes postmortem period. Although ischemia is marked by a fall in NAA, the fall in NAA was not evident in our study. The unchanged NAA/Cr ratio may be because Cr concentration was decreasing as well as NAA, or all transport mechanisms were shut down. Only at 24 hours was the Ins/Cr ratio markedly increased. Since Ins is a principal component of phospholipid that constitutes cellular membrane and organelles, the increase of inositol may indicate decomposition of phospholipid.

In conclusion, non-invasive, image-guided, localized, water-suppressed in vivo ^{1}H MRS from small contiguous regions of brain can be used to monitor the evolution of metabolic events in tumors, infarcted and surrounding tissues. Significant MR spectral differences between the infarcted and control regions were observed. A method that could precisely assign observed lesions to specific diagnostic categories (tumor or nontumor ; malignant or benign) could reduce the need for surgical biopsy and thus reduce patient morbidity and mortality. Observation of early changes in the NAA/Cr ratio and Lac signal intensity may allow the prediction of tissue viability at an earlier stage than now possibly MRI and clinical evaluation. Our results suggest that ^{1}H MRS could aid in better understanding the neuropathologic process of neoplastic tissue and time of death. This information, obtained noninvasively, might aid in making diagnosis, predicting prognosis, and monitoring and evaluating drug therapy.

Acknowledgments

We express our gratitude to Mr. Sang-Mook Lee, Mr. Ho-Gun Lee, Mr. Ho-Suck Chae, Mr. Sung-Hoon Chung, Mr. Byung-Hoon Ha and Mr. Byung-Sam Chung (Kangnam St. Mary's Hospital, Seoul, Korea) for technical support and patient treatment. Also, we are grateful to the Catholic University Medical Center (CUMC) staff, residents, interns, and medical students for their voluntary participation. This study was supported by the Research Fund of Korean Scientific Foundation (#951−0701−003−2) and '95 Schering Research Fellow ship for Diagnostic Radiology.

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양성자 자기공명분광법의 임상과 실험응용

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초 록

뇌종양, 뇌졸중, 정신분열증과 개뇌에 대하여 영상으로 정위선정하고 수분억제 방식을 이용한 양성자 자기공명분광법을 시행하였다. STEAM 펄스 시퀀스를 채택하여 GE Signa 1.5 T 전신 MRI/MRS system을 사용하였다. 크레아틴 (creatine)을 중심으로 양성자 대사물질의 비율을 Marquart 알고리즘을 이용하여 구하였다. 뇌이상조직의 생체내 양성자 자기공명 스펙트럼은 N-acetylaspartate (NAA), choline (Cho), lactate (Lac)의 신호 강도가 현격히 차이를 보였다. 본 연구의 결과는 양성자 자기공명분광에 의해 얻어진 대사물질의 비율은 뇌종양, 뇌졸중, 정신분열증 등의 지표로 사용할 수 있으며, 또 뇌사 판정 기준에 유용한 대사 정보를 제공할 수 있음을 시사해 주고 있다.