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Evaluation of thalamic neural activity in CRPS type 1 patients by proton MR spectroscopy: a correlative study with rCBF

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Proton magnetic resonance spectroscopy (^{1}H-MRS) is a useful noninvasive tool for chemical analysis in the brain in vivo [1–3]. ^{1}H-MRS can detect several important metabolites, such as *N*-acetylaspartate (NAA), choline (Cho)-containing compounds, and creatine plus phosphocreatine (total creatine: Cr) [1–3]. The ratio of *N*-acetylaspartate to creatine (NAA/Cr ratio) is considered to reflect neural activity in the brain [1–4]. In cerebral ischemic disease [1], Alzheimer's disease [2], and dementia [3], reduction of the NAA/Cr ratio has been confirmed.

Recent brain imaging studies have reported reduced thalamic blood flow in chronic neuropathic pain [5,6]. However, few studies have examined the neural activity of the thalamus of patients with chronic neuropathic pain using ^{1}H-MRS [7]. In this study, we examined the relationship between the NAA/Cr ratio and regional cerebral blood flow (rCBF) in the thalamus, using ^{1}H-MRS and stable xenon-enhanced computed tomography (xenon-CT) [8–10] in four patients with chronic complex regional pain syndrome (CRPS) type 1.

Four patients with chronic CRPS type 1 (all men, aged 35, 47, 47, and 48 years), who were referred to the Pain Clinic of the Department of Anesthesiology at Shiga University of Medical Science for assessment of neural activity using ^{1}H-MRS, participated in this study. Four patients who developed CRPS symptoms (ongoing pain, allodynia, vascular abnormalities, movement disorder, and trophic changes in skin and nails) suffered from longstanding, severe throbbing and burning pain (one in the right hand, one in the right leg, and two in the left leg). The duration of the pain was 1, 3, 3, and 6 years, respectively. The severity of pain was rated as 4 to 8 on a visual analogue scale (VAS) (0, no pain; 10, maximal pain). The pain was resistant to standard treatment, including nerve block and various medications (anticonvulsants, intravenous lidocaine, oral mexiletine, intravenous ketamine, and antidepressants).

To measure the neural activity of the thalamus, we performed ^{1}H-MRS with a 1.5-T SIGNA MR system (General Electric, Milwaukee, WI, USA) employing the standard circular polarized head coil. The $2 \times 2 \times 2$ cm volume of interest was selected in the bilateral thalamus region by axial T1-weighted MR imaging (Fig. 1). ^{1}H-MRS spectra were obtained by a simulated-echo method with chemical shift selective saturation pulse sequence with a repetition time of 6 s, an echo time of 300 ms, and 600 acquisitions. Positioning of each voxel was performed by an experienced neuroanatomist and adjusted to the thalamus of the individual brains. The spectra were analyzed with OMEGA software (GE Medical Systems, Milwaukee, WI, USA) at a SPARC workstation (SUN Microsystems, Milwaukee, WI, USA). The MR spectra constantly showed two major peaks corresponding to NAA and Cr (Fig. 2). We measured the NAA/Cr ratio (%), which reflects neural activity, in the four patients.

Measurement of rCBF by xenon-CT was conducted using the conventional protocol (a wash-in, 5 min wash-out method with 3 min inhalation of 30% xenon gas) at a transverse slice 5 cm above the orbitomeatal line (OM line) from a single CT slice at the level of the basal ganglia, including the thalamus [8–10]. The calculations of rCBF were semiautomatic and were performed with xenon-CT software.

The patients were informed about the measurement protocol, which was approved by the hospital ethical committee. Informed consent was obtained from all patients before measurement.

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We examined the correlation between the NAA/Cr ratio (%), measured by ^{1}H-MRS, and rCBF in the thalamus, measured by xenon-CT, in the four patients (n = 8). For statistical analysis, Spearman rank correlation coefficients were used to examine the relationship between the NAA/Cr ratio (%) and rCBF (ml·100 g^{-1}·min^{-1}) by xenon-CT measurement. $P < 0.05$ was considered to indicate statistical significance.

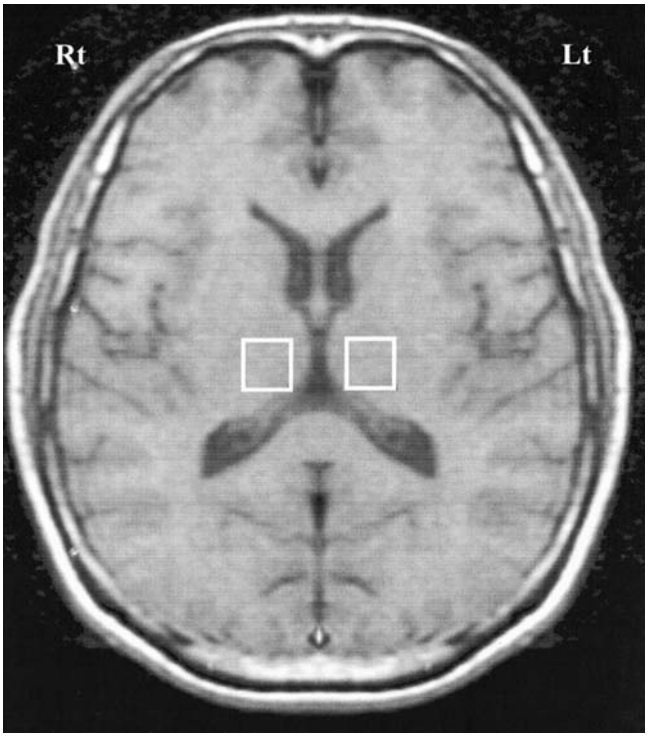

Fig. 1. T1-weighted proton magnetic resonance image in a patient with chronic neuropathic pain (complex regional pain syndrome; CRPS type 1). The *square* indicates the volume of interest (VOI), a 2 × 2 × 2-cm voxel in the thalamus in which ^{1}H-MRS was measured

The NAA/Cr ratios (%) in the thalamus contralateral and ipsilateral to the side of the pain in the four patients were 129:140, 123:132, 120:144, and 135:147. The rCBF values (ml·100 g^{-1}·min^{-1}) in the thalamus contralateral and ipsilateral to the side of the pain were 61.1:78.4, 48.4:60.1, 57.3:70.1, and 62.7:70.7, respectively. The NAA/Cr ratios (%) by ^{1}H-MRS measurement correlated significantly with the rCBF values (ml·100 g^{-1}·min^{-1}) by xenon-CT measurement (r = 0.88, $P < 0.05$) (Fig. 3).

^{1}H-MRS has been widely applied to various pathologic conditions, such as cerebral ischemic disease [1], Alzheimer's disease [2,11], and dementia [3], for neural activity research by noninvasive chemical analysis. Reduction of the NAA/Cr ratio, which has been confirmed in these diseases, has been considered to reflect a loss of neurons, neural degeneration, and neural dysfunction [1–4,12]. The NAA/Cr ratio is commonly used as an internal standard of neural activity [1–4,12]. However, few studies have examined chronic neuropathic pain using ^{1}H-MRS [7], although previous PET (positron emission tomography) [5] and SPECT (single photon emission computed tomography) studies [6] have reported decreased rCBF in the thalamus in patients with various types of chronic neuropathic pain.

Measurement of rCBF by xenon-CT offers much higher spatial resolution, allowing more precise reference of flow and providing quantitative information on rCBF in deeper regions of the brain [8–10].

In this study, the NAA/Cr ratios in the thalamus were significantly correlated with rCBF measured by xenon-CT. According to our results with ^{1}H-MRS, the neural activity of the thalamus in patients with chronic CRPS type 1 seems to be associated with rCBF.

Iadarola et al. [5], on the basis of a PET study, suggested that decreased thalamic activity contralateral to the symptomatic side may be a clinical feature common to a wide variety of chronic pain disorders. The patients with chronic CRPS type 1 showed a decreased NAA/Cr

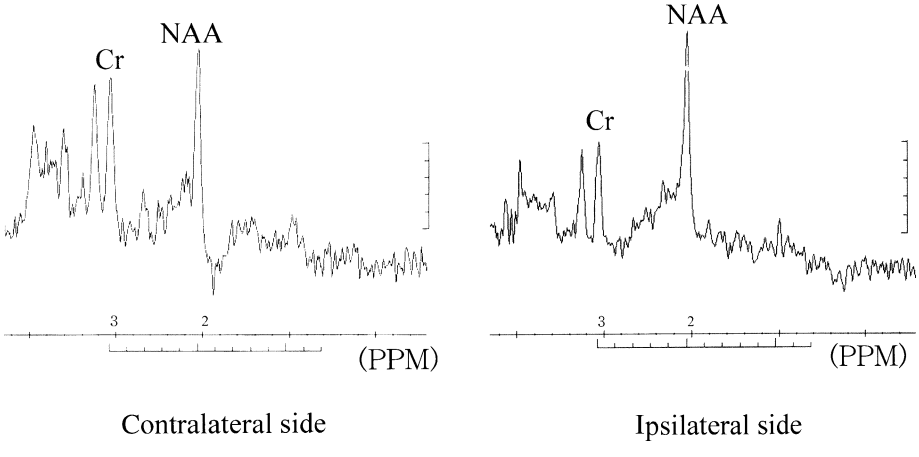

Fig. 2. ^{1}H-MRS of metabolites in the thalamus of a patient with chronic CRPS type 1. Contralateral to the side of pain (*left*) and ipsilateral to the side of pain (*right*). The ^{1}H-MRS spectra are usually characterized by three major peaks: NAA [*N*-acetyl-aspartate (NAA, 2.02 ppm)] and creatine plus phosphocreatine (Cr, 3.0 ppm). Chemical shifts are indicated in parts per million (ppm)

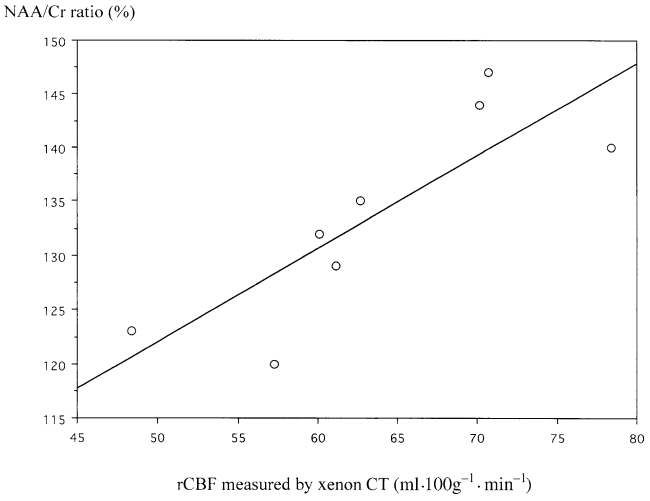

Fig. 3. Significant positive correlation of NAA/Cr ratios (%) with rCBF (ml·100 g^{-1}·min^{-1}) measured by xenon-CT (r = 0.88; $P < 0.05$). For statistical analysis, Spearman rank correlation coefficients were used to examine the relationship between the NAA/Cr ratios (%) by ^{1}H-MRS measurement and rCBF (ml·100 g^{-1}·min^{-1}) by xenon CT measurement. $P < 0.05$ was considered to indicate a statistically significant difference

ratio in the thalamus contralateral to the side of the pain as compared with the ratio on the patient's ipsilateral side.

Our results with the use of ^{1}H-MRS show that the neural function of the thalamus may be associated with rCBF. ^{1}H-MRS may serve as a useful noninvasive tool for evaluating thalamic neural activity in clinical practice.

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