Editorial

Central Nervous System Abnormalities in Fibromyalgia: Assessment Using Proton Magnetic Resonance Spectroscopy

Fibromyalgia (FM) is a prevalent musculoskeletal disorder for which progress in developing effective diagnostics and therapeutics has been hampered by an incomplete understanding of the underlying pathophysiology. The clinical syndrome is complex and variably expressed, but almost always features some degree of pain amplification. Interestingly, this hyperalgesia is not confined to pressure stimuli, but also involves heightened responses to heat, noise, and smell, suggesting an important role for central pain processing abnormalities[1].

The biological basis for the clinical phenomenology seen in FM remains elusive. Studies that have attempted to shed light on the biology of FM have focused particularly on the mechanisms underlying pain perception. The available data suggest that there are abnormalities in both peripheral and central pain mechanisms. Increased levels of substance P in peripheral tissues have been reported by some investigators and not others[1,2], and the muscles of FM patients exhibit ultrastructural abnormalities[3]. These abnormalities may contribute to an increase in nociceptive stimuli entering the spinal cord through the dorsal horn neurons and, in turn, being transmitted to the brain. Substance P levels have been shown to be elevated in the cerebral spinal fluid of patients with FM[4]. Ultimately, there is central sensitization to pain where low-intensity stimuli in peripheral tissues such as skin and muscle generate an exaggerated nociceptive response that is interpreted centrally as pain. The central mechanisms underlying this amplified pain perception have been explored using a number of advanced imaging techniques that aim to localize and characterize abnormalities in specific areas of the brain. These studies have focused on pain-processing areas of the brain that have been called the "pain matrix"[5].

Proton magnetic resonance spectroscopy (^{1}H-MRS) is a noninvasive method to examine changing tissue chemistry by examining the levels of important metabolites. N-acetylaspartate (NAA), choline (Cho), creatine (Cr), and lactate, considered key brain metabolites present at sufficient concentrations to be detected, are thought to provide information, respectively, on the status of neurons within the tissue, cell-wall metabolism, overall energy status, and anaerobic metabolism. A wealth of additional metabolites can be observed with a short echo time (TE) acquisition, including glucose, myoinositol, glutamine, glutamate, glycine, and others. A key advantage of ^{1}H-MRS is that it can be tagged onto a standard magnetic resonance imaging (MRI) study, so that the patient does not have to be scheduled for a separate imaging study as with single-photon emission-computed tomography or positron-emission tomography (PET). Other MRI studies that can be utilized are functional MRI (fMRI) to examine brain activation levels, diffusion tensor imaging to display white-matter fiber tract pathways, and perfusion imaging to examine the blood perfusion of brain tissue.

Data published by Emad, *et al* in this issue of *The Journal* highlight the application of ^{1}H-MRS to the *in vivo* assessment of metabolite levels in the brain of patients with FM[6]. The specific brain region chosen for the study was the hippocampus, as it is a key region of the limbic system involved in memory and cognition, and in inhibiting the stress response. Moreover, pain-related responses have been previously detected in the hippocampus of patients with irritable bowel syndrome using fMRI[7]. Spectra generated from ^{1}H-MRS studies of the hippocampus area in 15 patients with FM were compared to those of 10 healthy controls, and levels of NAA, Cho, and Cr were analyzed quantitatively from the spectra. Since Cr levels are known not to vary, these are typically used as an internal standard allowing the comparison of NAA/Cr and Cho/Cr ratios between study groups. The authors conclude that NAA levels are significantly lower and the Cho levels are higher in the hippocampus of FM patients compared to controls, although the Cho/Cr ratio did not differ significantly. Interestingly, these differences were much more pronounced when com-

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paring spectra from the right hippocampus than the left. The authors speculate that the lower NAA levels seen in the FM patients may represent evidence of neuronal or axonal metabolic dysfunction, and since the hippocampus plays a role in cognitive functions, sleep regulation, and pain perception, it is proposed that these metabolic abnormalities in the hippocampus relate to clinical symptoms observed in these domains.

While provocative, these findings need to be interpreted with considerable caution. In visually evaluating the spectra presented in the appended figures, the height of the metabolite peaks compared to the height of the noise peaks indicates a low signal-to-noise ratio (SNR). This is a particularly important technical aspect of ^{1}H-MRS, since all data interpretation is dependent on the quality of the spectra. Currently available spectral analysis tools provide a measure of the ability to discern the spectral peak in the noise background (called the Cramer-Rao lower bound) below which the metabolite cannot be reliably measured. There is no indication that this type of analysis has been applied to analysis of the raw spectra. Another key issue is that of absolute quantification of metabolite levels. The generation of meaningful quantitative ^{1}H-MRS requires additional corrections for differences in coil-loading, T2 relaxation effects, T1 relaxation effects, and partial volume effects. None of these corrections are stated in the Materials and Methods. On the other hand, more reliable conclusions can potentially be drawn from the calculated metabolite ratios such as NAA/Cr and Cho/Cr since these involve an internal "control"; however, due again to the low SNR of the spectra, these data are also questionable. The use of a very long TE of 272 ms limits the number of useful metabolite peaks that can be measured, and also makes the acquisition sensitive to changing T2 relaxation times of the individual metabolites.

Despite these significant technical issues regarding acquisition and analysis of the ^{1}H-MRS spectra, the findings of Emad, *et al* are broadly consistent with those of Petrou, *et al*, who recently demonstrated that the Cho/Cr ratio in the dorsolateral prefrontal cortex (DLPC) of FM patients was positively correlated with visual analog scale pain[8]. In contrast, analysis of data from the insula and basal ganglia regions in their FM patients demonstrated that the NAA/Cho ratios were negatively correlated with pain threshold levels. Importantly, this study did not demonstrate any overall differences between the FM patients and the controls with respect to the NAA/Cr or the Cho/Cr ratio. This latter finding is difficult to relate to the findings in the Emad study, since the neuroanatomical areas studied differed, and a NAA/Cho analysis was not presented in the latter study. Of relevance, a study of patients with chronic low back pain had previously demonstrated that the NAA levels were reduced in the DLPC of these patients compared to controls[9].

In assessing functional characteristics in the central nervous system (CNS) of FM patients using techniques such as fMRI and ^{1}H-MRS, it is particularly informative to evaluate changes in the measured characteristics in response to painful stimuli, and compare these to normal controls where possible. Using fMRI assessments, Gracely, *et al* previously demonstrated that painful stimuli that were perceived as subjectively comparable in FM and control subjects resulted in activation patterns that were similar, whereas objectively similar levels of stimulation resulted in no common regions of activation, and greater effects in patients[10]. This finding was consistent with the hypothesis that there is a subcortical augmentation of pain processing in FM patients. In a more recent study that combined fMRI and ^{1}H-MRS assessments in 10 FM patients, the CNS changes in response to painful stimuli were evaluated before and after acupuncture, a non-pharmacologic intervention to reduce pain[11]. The investigators focused their ^{1}H-MRS measurements on the insula region of the CNS, an area adjacent but lateral to the hippocampus, that is particularly important in processing pain and assigning an affective component to the stimulus. The ^{1}H-MRS spectra from this study demonstrated a positive correlation between changes in clinical pain ratings and changes in glutamate (Glu)/Cr ratio, whereas there was no correlation between changes in clinical pain perception and NAA/Cr or Cho/Cr ratios. Since Glu is a major excitatory neurotransmitter, this association was perhaps not unexpected. Interestingly, the changes in blood oxygenation level-dependent activation, as measured by fMRI, positively correlated with the changes in Glu/Cr ratio, but only on the contralateral insula region. Again, as with the Emad study, these data point to major differences in metabolic activity of the same neuroanatomical structure on opposite sides of the brain.

The application of ^{1}H-MRS to the study of CNS metabolic function *in vivo* in disorders such as FM is exciting and hypothesis-generating, but is fraught with methodological and technical problems. To date, all the studies, perhaps by necessity, have been small and likely underpowered. There have been few attempts to provide a rationale for the number of patients and controls needed to detect truly meaningful differences. On the other hand, if one tries to amalgamate the datasets from different studies, the problem of voxel placement becomes immediately apparent. Each study provides a rationale for why a particular area of the brain was studied, but there is no consistency as to which "window" should be used to look into the brain's function to define dysfunction. Even if voxel placement were standardized by some form of consensus process, such as that used by OMERACT (Outcome Measures in Rheumatology)[12,13], the generation of reliable quantitative data from the ^{1}H-MRS spectra remains challenging. As discussed above, the SNR in these studies may preclude any meaningful interpretation of the data. Finally, and perhaps most importantly, the case definition of FM remains challenging. Since the hallmark of

this syndrome is a subjective phenomenon based on aberrant pain perception, assembling a relatively homogenous population of patients is difficult. The American College of Rheumatology criteria[14] provide the basis for selecting individuals to include in studies, but clinical experience clearly indicates that there are marked differences between individuals as to how they perceive pain, and even in the same individual at different times.

The brain will not reveal its secrets easily, particularly when subjective perceptual phenomena are being studied. The recent assault on this tissue using minimally invasive techniques such as fMRI, PET, and ^{1}H-MRS has been impressive, but the results are still of modest clinical significance. The identification of reproducible CNS biomarkers that will enhance our understanding of the mechanisms underlying FM, and potentially aid in clinical diagnosis and treatment, remains an achievable, but unrealized goal. Increased consensus regarding patient selection, sample size, and standardization of technically demanding approaches such as ^{1}H-MRS is needed to make progress towards this goal.

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