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BACKGROUND AND PURPOSE: **Spinal cord injury (SCI) results in a number of consequences; one of the most difficult to manage is chronic neuropathic pain. Thus, defining the potential neural and biochemical changes associated with chronic pain after SCI is important because this may lead to development of new treatment strategies. Prior studies have looked at the thalamus, because it is a major sensory relay station. The purpose of our study was to define alterations in metabolites due to injury-induced functional changes in thalamic nuclei by using single-voxel stimulated echo acquisition mode MR spectroscopy.**

METHODS: **Twenty-six men were recruited: 16 patients with SCI and paraplegia (seven with pain, nine without pain) and 10 healthy control subjects. Pain was evaluated in an interview, which included the collection of information concerning the location, quality, and intensity of pain, carefully identifing the dysesthetic neuropathic pain often seen in SCI. Localized single-voxel (8-cm^3 volume) proton spectra were acquired from the left and right thalami.**

RESULTS: **The concentration of *N*-acetyl (NA) was negatively correlated with pain intensity ($r = -0.678$), and the *t* test showed that NA was significantly different between patients with pain and patients without pain ($P = .006$). *Myo*-inositol was positively correlated with pain intensity ($r = 0.520$); difference between patients with pain and those without pain was almost significant ($P = .06$).**

CONCLUSION: **The observed differences in metabolites in SCI patients with and pain and in those without pain suggest anatomic, functional, and biochemical changes in the thalamic region.**

Results from recent studies (1–8) support the high incidence of chronic pain after spinal cord injury (SCI) as well as high pain intensity ratings in patients with SCI. Despite increased understanding of the mechanisms responsible for the different types of pain after SCI (9, 10), no treatment approaches have been proven to be consistently effective in treating or managing central neuropathic pain after SCI. Because chronic pain after SCI is heterogeneous (6, 8, 11, 12), an extensive verbal pain evaluation and neurologic examination is needed to determine the specific type and severity of the pain. One of the primary objectives in understanding the central mechanisms of SCI pain has focused on the delineation of anatomic, neurochemical, and functional changes at or adjacent to the site of injury (13–16). When the many changes that occur in the cord after deafferentation of central neurons (17–19) are considered, these alterations may possibly play an important role in the development of SCI induced pain. An important observation regarding the central mechanism of pain after SCI appeared in a report (20) describing the increase in spontaneous neuronal activity as well as burst discharges in thalamic nuclei of a patient with chronic SCI-related pain. In another study (21), significant increases in blood flow were observed in thalamic nuclei during the sensation of pain, whereas blood flow in these nuclei decreased during non-pain periods.

Although changes in blood flow can be used as a reflection of neuronal activity in different brain struc-

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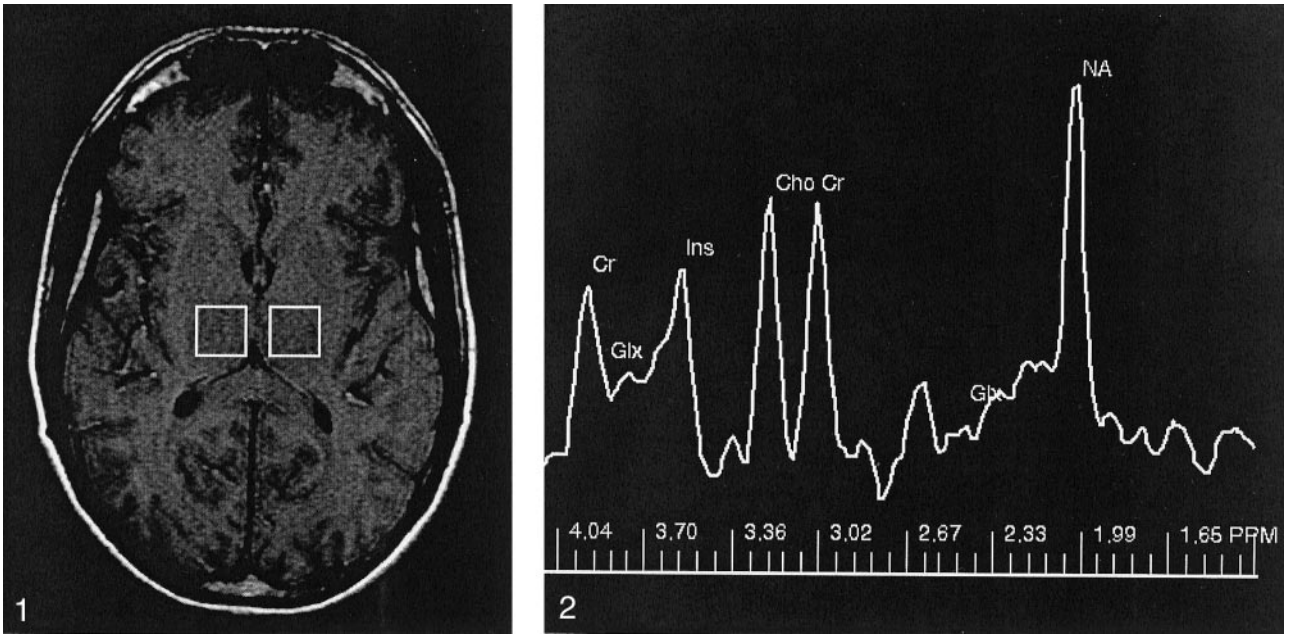

FIG 1. Axial T1-weighted image shows the location of the 2 × 2 × 2-cm voxel in the region of the left thalamus and the corresponding location of the right thalamus. MR spectroscopic data were separately acquired from each voxel for the three groups: SCI patients with pain, SCI patients without pain, and healthy control subjects.

FIG 2. Typical single-voxel stimulated echo acquisition mode spectrum from a healthy control subject. The assignment of peaks to various cerebral metabolites and the spectral analysis are described in Methods.

tures, other potential signatures of the pathophysiologic changes in the brain are the biochemical changes, as determined by using MR spectroscopy. MR spectroscopy can be used to noninvasively measure the in vivo concentration of metabolites in the human brain. To our knowledge, no MR spectroscopic study has been performed to assess alterations in brain metabolites in patients with SCI and chronic neuropathic pain.

The purpose of the present study was to test the hypothesis that MR spectroscopy can be used to detect changes in cerebral metabolites in the thalami of patients with chronic neuropathic pain after SCI.

Methods

Patients

Twenty-six men participated in the study. Sixteen patients with SCI had paraplegia: seven (mean age ± SD, 46.2 years ± 16.2) had chronic pain (SCI with pain group), and nine (34.8 years ± 10.0) had no pain (SCI without pain group). Ten healthy men (42.3 years ± 10.5) served as control subjects. The mean elapsed time since injury for the group of SCI patients with pain was 7.6 years ± 6.3 and 11.3 years ± 9.6 for the group of patients without pain. For the SCI group with pain, the distribution of patients according to their level of injury was as follows: One had an injury at the C8 level, and six had an injury at T9–L3 levels. For the SCI group without pain, the following distribution was found: Four had an injury at the C4–C8 levels, and five had an injury at the T7–L3 levels. Informed consent was obtained in accordance with the guidelines of the human subject committee of our institutional review board.

Pain Evaluation

Pain was evaluated according to the method used in a previous study (8). For the location of pain, the patients were asked to mark, on a pain drawing (8), the areas corresponding to the chronic pain that they were presently experiencing. The pain drawing was divided into eight principal areas: 1) head, 2) neck and shoulders, 3) hands and arms, 4) frontal torso and genitals, 5) back, 6) buttocks, 7) thighs, and 8) legs and feet. The participants were asked to describe the location of the pain and, if possible, to mark the pain that they perceived as most disturbing on a separate pain drawing. To assess the quality of pain, the patients were asked to select sensory words (8) from a list that best described the pain they were presently experiencing.

Pain intensity was assessed by using a numerical rating scale (NRS) with scores ranging from 0, which indicated no pain, to 10, which indicated most intense pain imaginable. In some of the analyses, an average pain intensity was used. This variable was obtained by averaging the most intense pain score and least intense pain score. Pain intensity was evaluated immediately before, during (in the middle), and immediately after the MR imaging–MR spectroscopic study. These evaluations were performed to assess any change in the level of pain intensity during the MR imaging–MR spectroscopic study.

MR Imaging and Spectroscopy

All three groups of patients underwent imaging on a 1.5-T whole-body MR imaging system. A quadrature body coil was used as a transmitter, and a quadrature head coil was used as a receiver. Axial T1-weighted spin-echo images (650/20/1 [TR/TE/NEX]), T2-weighted fast spin-echo images (3500/112/1 [TR/TE_{eff}/NEX]), and fast fluid-attenuation inversion recovery images (6000/128/1; TI, 2000 ms) were obtained with the same section thickness (5 mm), gap (1.5 mm) FOV (220 mm), and matrix (192 × 256). For the purpose of voxel placement, additional parasagittal and coronal T1-weighted spin-echo pilot images (200/20/1) were acquired with a section thickness of 5 mm, a FOV of 220 mm, and a matrix of 128 × 256 in the region of the thalami. Localized proton spectra were acquired from the left and right thalami by using a 8-cm^3 voxel (Fig 1). MR spectra were acquired by using a single-voxel stimulated echo acquisition mode pulse sequence (1500/20;

Metabolite concentrations in patient group versus those in control group

Group	Mean NA (nmol) ±SD	Mean Ins (nmol) ±SD	NA/Ins Ratios ±SD
Control	6.305 ± 0.347	2.659 ± 0.542	2.474 ± 0.579
SCI without pain	6.566 ± 0.409	2.263 ± 0.313	2.957 ± 0.467*
SCI with pain	6.052 ± 0.206†	2.886 ± 0.699‡	2.182 ± 0.418§

Note.—NA indicates *N*-acetyl; Ins, *myo*-inositol; SD, standard deviation; SCI, spinal cord injury.
*P = .06, compared with normal controls.
†P = .006, compared with SCI without pain.
‡P = .06, compared with SCI without pain.
§P = .004, compared with SCI without pain.

mixing time, 13 ms), with 256 averages, a bandwidth of ±1000 Hz, and 2048 data points.

Spectral analysis was performed by using the linear combination model (LCModel) software (22), a user-independent time-domain fitting routine that uses a basis set of concentration-calibrated model spectra of individual metabolites to estimate the absolute concentrations of similar brain metabolites from in vivo spectral data. This method exploits the full spectroscopic information of each metabolite and not just isolated resonances (Fig 2). The LCModel method yields concentrations for *N*-acetyl (NA), total creatine (Cr), choline compounds (Cho), glutamate (Glu), Glutamine (Gln), Glu and Gln (Glx), and *myo*-inositol (Ins). To account for patient-to-patient variability in coil loading, the unsuppressed water signal for each patient was divided by the mean of the water signal for all individuals, and this ratio was divided by the concentration results for that patient. Each metabolite was correlated with measures of pain intensity (Pearson correlation matrix). Post hoc *t* tests were performed to evaluate differences between the groups. *P* values of less than .05 were considered to indicate a significant difference.

Results

Pain Location and Descriptors

The patient's markings on the pain drawings showed that 29% (2/7) of the patients had pain in the neck and shoulders; 43% (3/7), in the upper extremities (arm, forearm, and hand); 50% (7/14), in the front and back of the chest and abdomen; 43% (3/7), in the buttocks; and 86% (6/7), in the thigh and lower extremities (leg and foot).

The words selected by the patients with SCI to describe the type of pain they experienced showed that 57% (4/7) had sharp pain sensations, and 86% (6/7) had burning, aching, and/or electric sensations commonly associated with neuropathic pain.

Using the NRS guidelines, we asked the patients to assign a number to the episode of least pain and the episode of the most pain that they had experienced since the time of injury. The average scores for the least intense pain and the most intense pain showed that 14% (1/7) of the patients had average pain intensity of 5 or less and that 86% (6/7) had pain intensity of greater than 5. The same questions were asked on the day of the MR study, and all seven patients had pain intensity of greater than 5. Pearson correlation analyses were performed; the results showed there was no correlation between the location of pain and the pain intensity.

MR Spectroscopy

For all individuals, MR spectroscopic data were acquired from the left and right thalami. Statistical analysis revealed no significant difference between the two sides, for each of the metabolite concentrations. Thus, in each individual, the concentrations for the two sides were averaged for each metabolite. For all patients with SCI, a Pearson correlation analysis was performed for each metabolite to evaluate trends. The analysis showed that NA was negatively correlated with the average pain intensity ($r = -0.678$) and that Ins was positively correlated with the average pain intensity ($r = 0.520$). No correlations were found for all the other metabolites (Cho, Cr, and Glx). The mean NA and Ins concentrations and the standard deviations, for the three groups, are shown in the Table. The ratio of NA to Ins (NA/Ins) was also computed, because these metabolites exhibited an opposite correlation with respect to pain intensity. The differences in metabolites between the three groups of patients were not apparent on visual inspection of the spectra.

For NA, the *t* test showed that difference between healthy control subjects and the SCI patients without pain were not significant; however, a trend toward significance was observed between healthy control subjects and SCI patients with pain ($P = .08$). The difference between SCI patients with pain and those without pain was significant ($P = .006$). For Ins, the difference between healthy control subjects and SCI patients with or those without pain was not significant. However, the Ins difference Ins in SCI patients with pain compared with those without pain was nearly significant ($P = .06$). Differences in the NA/Ins ratio approached significance in healthy control subjects compared with SCI patients without pain ($P = .06$), and the ratio was significantly different between SCI patients with pain compared with SCI patients without pain ($P = .004$).

Discussion

SCI results in a number of consequences that can have a devastating effect on individuals who are dealing with the complications of a traumatic injury to the central nervous system (8, 23). One of the consequences that was rated most difficult to manage is the

onset of chronic pain. In recent studies (1, 8, 23, 24), the prevalence of pain associated with SCI was reported to be 60–80%. More important, however, is the influence of this pain on the patient's quality of life. For example, pain was reported to interfere with daily activities, including work, exercise, and social interactions, in 664 (83%) of 800 patients who responded to the postal survey conducted by Nepomuceuno et al (25). The importance of SCI pain is further underscored by the fact that nearly 40% of patients in this study stated they would trade any likelihood of physical recovery for the relief of pain.

Of the different types of pain associated with SCI, the most challenging for patients and health professionals is pain in parts of the body that lack normal sensation, with a spontaneous and persistent clinical profile. This type of pain is often described as burning, shooting, throbbing, and stabbing (4, 8, 24). Although the condition of pain after SCI was first described more than a century ago, little is known about the pathophysiology underlying the onset and persistence of this condition. One of the primary objectives in understanding the central mechanism of SCI-related pain is the delineation of the anatomic, neurochemical, and functional changes in the spinal cord at or adjacent to the site of injury (13–16). Although focusing on the spinal cord might seem logical, less attention has been paid to what may be a notable consequence of SCI, namely, the effect of the injury on certain regions of the brain that become functionally and anatomically disconnected from the spinal cord. When the many changes that occur after deafferentation of central neurons (17–19) are considered, these alterations in the functional state, which are secondary to deafferentation, may possibly play an important role in the development of SCI-induced pain.

An important observation regarding the central mechanism of pain after SCI appeared in a report (20) that described the increase in spontaneous neuronal activity as well as burst discharges in thalamic nuclei of a patient with chronic SCI-related pain. The conclusion from this study was that spinal injury resulted in the deafferentation of thalamic neurons and the emergence of abnormal seizure-like discharges. A second observation related to the role of thalamic structures in SCI pain was made by using the technique of single photon emission computed tomography (SPECT) (21). In an SCI patient with intermittent pain, significant increases in blood flow were observed in the thalamic nuclei during the sensation of pain, whereas blood flow decreased in these nuclei during non-pain periods. Given the fact that increased blood flow has been shown to be correlated with an increase in neuronal activity and/or abnormal discharges of CNS neurons (26), the results of the SPECT study are consistent with the recording studies of Lenz and colleagues (20).

Several MR spectroscopic studies (27–29) have shown that regional decreases in NA levels occur in patients with brain tumors, epilepsy, metabolic brain disorders, or neurodegenerative disorders such as amyotrophic lateral sclerosis (ALS) and Huntington and Parkinson diseases. NA is thought to be localized in neurons and neuronal processes in the mature brain, and NA concentrations are decreased in several types of cerebral diseases; such decreases are interpreted as reflections of neuronal dysfunction. The SCI patients with pain had decreased NA levels compared with those in control subjects and SCI patients without pain. A possible explanation for decreased NA concentrations in SCI patients with pain may be dysfunction of inhibitory neurons due to deafferentation. Correspondingly, the loss of inhibitory control may result in greater activity of excitatory neurons and a heightened sensation of pain. The results from the assessment of pain location and descriptors showed that 86% of the patients had pain in the thigh and lower extremities; this location was below the expected level of sensation based on the site of injury. Also, 86% of the patients had burning, aching, and electric sensations in the thigh and lower extremities; these findings suggested that the patients with SCI had neuropathic pain.

Myo-inositol is thought to be a glial marker and an organic osmolyte that plays a major role in the osmoregulation of astrocytes (30). *Myo*-inositol has been shown to be increased in the precentral gyrus of patients with ALS compared with healthy subjects (28). We found that the overall concentrations of Ins were lower in SCI patients without pain compared with those in healthy control subjects and SCI patients with pain. Also, the difference in Ins concentration between SCI patients without pain compared with SCI patients with pain approached significance. These results may reflect differential alteration of glial cells (gliosis) in the thalami.

Because NA concentrations decrease and Ins concentrations increase with pain intensity, the NA/Ins ratio may be a clinically useful tool for assessing pain resulting from SCI. For example, the NA/Ins ratio may be sensitive in predicting the early effectiveness of new therapeutic strategies for managing pain in SCI patients.

Our study has some limitations. First, the mean age of the SCI patients without pain was lower than that of the other two groups; this difference could have resulted in age-dependent differences in NA or Ins. Several studies (31–33), however, have shown that cerebral metabolic changes with aging occur almost entirely within the first 2 years of life. Only minimal changes occur thereafter, and adult concentrations are achieved at the age of 20 years (34). Thus, the age differences between groups in this study are unlikely to account for the observed metabolic changes. Second, the patients enrolled in our study were all men. This selection was used because studies (35) have shown that sex-related differences in the perception of pain exist. Third, only the SCI patients with chronic pain were receiving anticonvulsants or analgesics daily. The three most common medications were gabapentin, baclofen, and ditropan. Their potential effect on the levels of metabolites detectable with MR spectroscopy has not been fully investigated; however, we (28) have reported that metabolite levels, includ-

ing NA and Ins levels, did not differ in ALS patients treated with gabapentin, as determined before and 2 weeks after gabapentin treatment. A more extensive investigation of potential effects of pain medication on the levels of cerebral metabolites was beyond scope of our investigation.

Conclusion

Our findings show that MR spectroscopy can be used to detect thalamic metabolic changes in patients with SCI. The concentration of NA is lower in SCI patients with pain compared with that in SCI patients without pain and healthy control subjects. Because NA is a neuronal marker, patients with SCI and chronic pain may have a higher degree of dendritic pruning or neuronal loss or dysfunction, compared with control subjects or SCI patients without pain. Ins concentrations were lower in SCI patients without pain than in healthy control subjects or SCI patients with pain; this finding possibly reflects differential effects on glial cells in the thalamus in response to SCI.

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