Regional Heterogeneity of Post-Traumatic Brain Metabolism as Studied by Microdialysis, Magnetic Resonance Spectroscopy and Positron Emission Tomography

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INTRODUCTION

Traumatic brain injury (TBI) results in primary damage to selected brain regions immediately or within a few minutes. This injury is generally easily recognized on computerized tomographic scans taken in the emergency room, and is often the target of emergency surgery. However, adjacent tissue may be variably damaged in the acute process or as a result of secondary insults. The pathological changes in this adjacent tissue have been best characterized by imaging (11-13) and by studies of brain metabolism (4). In addition, widespread disturbances of brain metabolism with regional heterogeneity exist after experimental TBI and human TBI. The significance of focal pathology on the metabolism of the surviving surrounding brain tissue is not well appreciated. Unfortunately, this regional variation of metabolism may not be static and may change over time (3). Thus, monitoring brain metabolism during the acute injury period is difficult to do with neuroimaging alone.

The ability to selectively monitor surrounding tissue has recently been studied using positron emission tomography (2, 7, 10) and continuous monitoring may be possible using cerebral microdialysis (5, 9, 10, 14, 18). Cerebral microdialysis offers an indirect method of monitoring brain metabolism by looking at changes in the extracellular substrates and products of metabolism. The enhanced temporal resolution of cerebral microdialysis is offset by the confined regional specificity of the technique, with a sampling tissue volume of 1 to 2 cm³. However, strategically placed microdialysis catheters may offer continuous monitoring of a specific region of interest over time.

The purpose of this paper is to delineate, using 3 case examples, the ability of cerebral microdialysis to provide continuous monitoring of regionally heterogeneous brain glucose metabolism. Regional neurochemical heterogeneity of glucose metabolism is confirmed by using fluorodeoxyglucose positron emission tomography (FDG-PET) and proton-magnetic resonance spectroscopy (H-MRS).

METHODS

The present study was an observational trial approved by the University of California, Los Angeles institutional review board for human research. Five patients with severe TBI (Glasgow Coma Score<8, brain contusions on CT scan, intracranial pressure monitored) were studied using cerebral microdialysis, MRS and FDG-PET. The methods of cerebral microdialysis (18) and FDG-PET (4) have been previously described. Briefly, the patients had microdialysis catheters placed adjacent to an external ventricular drain and in normal tissue adjacent to the primary contusion; each catheter was perfused with normal saline at 2 uL/min. Sequential 1-hour samples of 120 uL were taken for 7 days. During the initial 72 hours, an FDG-PET scan was performed using a dynamic quantitative technique. A single intravenous injection of 10 mci 2-deoxy-glucose was made followed by a 3-dimensional dynamic acquisition using 18 frames (4 × 30 seconds, 4 × 120 seconds, and 10 × 300 seconds) and serial arterial and venous blood draws. Calculation of regional glucose metabolic rates in a 2 cm² region of the cerebral microdialysis probe were made after co-localization of the probe. The probe location was co-registered with the PET using MRI and/or CT images on which the probe could be seen. Immediately after FDG-PET scan, an MRI with MRS was performed using a 1.5 Tesla magnet (Sonata, Seimens Corporation). Conventional imaging consisted of axial T1 weighted and T2 weighted images of 5-mm slice thickness and slice separation of 7.5 mm. Proton spectra were obtained using multiple voxel spectroscopic imaging with long echo times (TR 1500, TE = 135 msec). A single slice that incorporates the middle of the focal contusion was used for the MRS, yielding 120 individual voxels of 1.5 cm³ size. Water and lipid shielding were performed to maximize signal to noise ratios. Excellent spectra were obtained with identifiable peaks. Automated quantitative values for lactate, choline, N-acetyl aspartate (NAA), and creatine (Cr) were obtained for each voxel. Ratios of NAA/Cr and lactate/Cr in pericontusional and normal appearing white matter (NAWM) were also compared. Thus microdialysis, FDG-PET and H-MRS each sampled a similar volume of tissue (1.5 cm³). Univariate analyses of variance for differences in microdialysis values, CMRglucose values and MRS values were performed to determine important regional differences.

RESULTS

Five patients with severe traumatic brain injury, GCS<8, underwent MRS and cerebral microdialysis. The patients were studied starting within 12 hours of injury with serial measurements, until 10 days after injury. The patients all suffered intraparenchymal contusional injuries in the frontal lobes with variable size of the contusions ranging from 25 to 60 cm³. All

Ipsilateral H-MRS
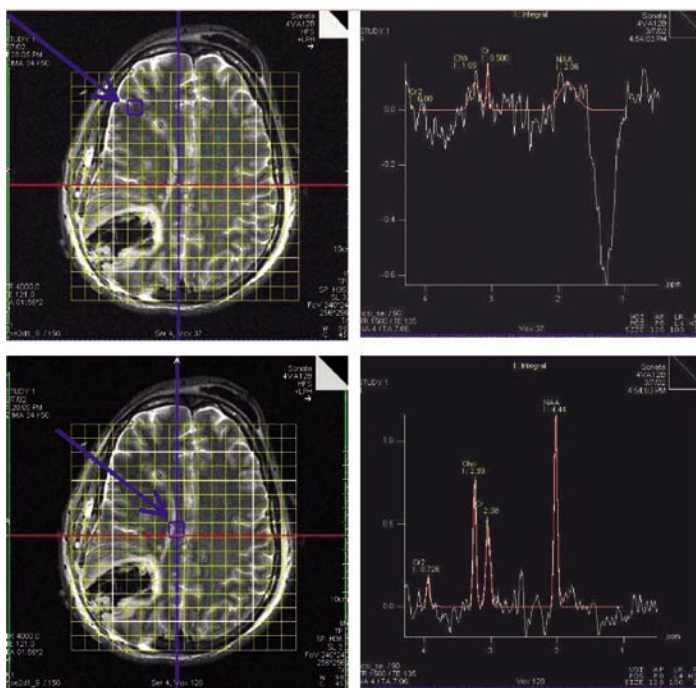
Contralateral H-MRS
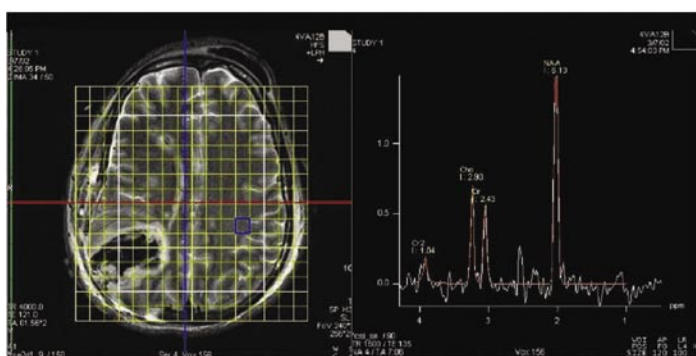
Figure 1. *Combined MRS and microdialysis in three regions after traumatic brain injury and corresponding FDG-PET scan.*
Top Panel left: MRI T2 localizing image with MRS grid highlighted to show voxel adjacent to microdialysis probe 1. Note that adjacent spectra demonstrates a reduced NAA and a prominent lactate peak at 1.3 ppm.
Top Panel Right: Corresponding microdialysis hourly samples showing low glucose and elevated lactate extracellular levels in the same voxel.
Middle Panel left: MRI and MRS in voxel adjacent to microdialysis probe 2 demonstrating normal NAA values and absence of lactate peak. Middle Panel right: Microdialysis hourly samples from probe 2 showing normal glucose and lactate extracellular levels in the same voxel.
Bottom Panel left: MRI and MRS in pericontusional tissue showing a lactate peak and reduced NAA.
Bottom Panel right: Corresponding FDG-PET scan showing increased glucose uptake in pericontusional tissue that has evidence of lactate on MRS.

patients required surgical evacuation of primary hemorrhagic contusions. Pathological specimens demonstrated necrotic brain interspersed with viable tissue, hemorrhage and scant mononuclear inflammatory cell infiltrates. Two of the 5 had persistent increased intracranial pressure (ICP)>20 mm Hg and all required CSF drainage to manage ICP. Four of the 5 made a good outcome with 6 month Glasgow Outcome Score of >4, whereas care was withdrawn in the third patient, which resulted in death.

MRS imaging done simultaneously with cerebral microdialysis was done in all 5 patients. In these patients, multivoxel MRS was done at the level containing the contusion and a separate slice containing the microdialysis probe. Representative spectra were obtained from 3 possible regions in each patient. The 3 regions were normal appearing white matter, pericontusional tissue and in the region of the microdialysis probe (adjacent to the ventriculostomy). In general the NAA values were lowest in the pericontusional tissue compared with normal appearing white matter (NAWM)(p<0.001).

Microdialysis values varied among subjects, making it difficult to compare tissue types in this small population. However, 3 patients underwent dual probe microdialysis with sampling of the pericontusional tissue and normal appearing white matter. Regional heterogeneity of cerebral microdialysis profiles for glucose and lactate was found. The microdialysis glucose values were higher (0.34 ± 0.11 versus 0.11 ± 0.03 mmol) and microdialysis lactate values lower (0.5 ± 0.2 versus 1.2 ± 0.17 mmol) in NAWM in comparison to pericontusional tissue.

Patient	Pericontusional	Ipsilateral NAWM	Contralateral NAWM
Patient 1			
NAA	0.50	4.40	4.20
NAA/Cr	0.95	1.76	2.40
Cho/Cr	0.88	1.20	1.22
FDG-PET	6.20	3.90	3.60
Patient 2			
NAA	0.60	3.40	3.50
NAA/Cr	0.88	1.71	1.00
Cho/Cr	1.06	1.18	0.98
FDG-PET	8.20	4.60	4.50

Table 1. The distribution of the MRS and PET data from two patients with combined studies.

Ipsilateral H-MRS
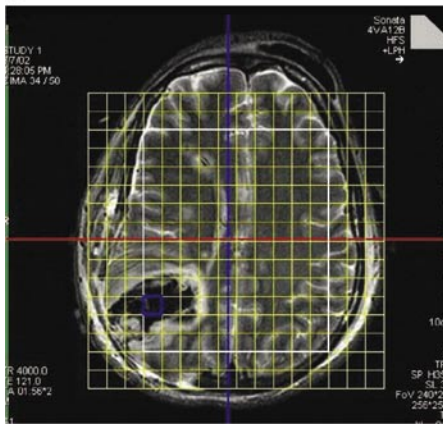
Contralateral H-MRS

Figure 2. MRI T2 image at the level of the brain contusion superimposed with quantitative values for selected compounds from each voxel. The quantitative values of lactate from each voxel were aligned in a table, the table size adjusted to the corresponding voxel siz, shade calibrated in pink, then overlaid on the imaging region. There is regional heterogeneity of the lactate values with pericontusional tissue demonstrating high levels of total tissue lactate.

Regional metabolic rates for glucose (CMRglucose) values were obtained from FDG-PET scans in 3 of the 5 patients. The CMRglucose values ranged from 3.5 to 9.4 mg/100 kg/min in regions containing the microdialysis probe. In 2 patients with regional increased glucose metabolism in pericontusional regions (6.2 and 8.8 mg/

100kg/min), microdialysis glucose was low (<0.2 mmol/l). By comparison, in NAWM the FDG-PET demonstrated decreased CMRglucose (3.2 and 3.4 mg/100 kg/min) and the corresponding microdialysis glucose was in the normal range (0.4-0.6 mmol/l). Corresponding microdialysate lactate was increased (to levels 1.5 mmol) in one of 2 patients with increased CMRglucose in pericontusional tissue. Figure 1 shows an example of combined H-MRS, FDG-PET and microdialysis in a patient with a right parietal contusion. This example demonstrates high levels of CMRglucose and elevated MRS lactate levels in the pericontusional tissue whereas the NAWM has reduced glucose metabolism, higher levels of NAA and corresponding normal range of microdialysis glucose and lactate levels. Moreover, the region surrounding the ventriculostomy demonstrates elevated microdialysis lactate and reduced glucose in combination with increased CMRglucose. Hence this patient demonstrates marked metabolic heterogeneity.

MRS imaging done within 24 hours of the PET scans in 2 patients demonstrate reduced NAA/Cr (<4) and increased Cho/Cr (<3) ratios in the pericontusional tissue. The NAA/Cr ratios were lowest in the pericontusional tissue in comparison to ipsilateral NAWM and contralateral NAWM. Table 1 shows the values obtained. In addition, a lactate signal was seen in pericontusional areas. In both cases, microdialysis lactate was elevated (>1.4 mmol) in the same region that demonstrated a MRS lactate signal. On FLAIR MRI the pericontusional tissue demonstrated the consistent finding that increased signal intensity occurred in the regions containing H-MRS lactate sig-

nals. Figure 2 demonstrates a regional map of lactate values within the H-MRS grid at the level indicated by the corresponding anatomical image. The lactate is elevated near the region of contusion, but is also present in remote areas.

DISCUSSION

The main preliminary findings contained in this paper are as follows: *i)* there is marked heterogeneity of brain glucose metabolism and neurochemistry in the traumatized brain during the initial week after injury; *ii)* pericontusional tissue demonstrates the lowest NAA levels, microdialysis glucose levels, and evidence of increased glucose metabolism compared with remote regions of the brain white matter; *iii)* multiple methods of measuring brain metabolism provide converging lines of evidence that the heterogeneity of post-traumatic brain metabolism exists and that whole brain analysis methods may average out these important differences; and *iv)* cerebral microdialysis provides longitudinal data about brain metabolism that can be confirmed by whole brain measures of brain chemistry and metabolism.

TBI results in a heterogeneous distribution of injury and metabolic dysfunction with some areas immediately irreversibly injured and other areas affected to a variable degree. Widespread alterations in brain metabolism and neurochemistry have been documented by various techniques, including PET, microdialysis and MRS. Pathologically, tissue is disrupted both in the primary injury site and in remote areas that otherwise appear normal. Tissue edema, hemorrhage, demyelination and cell death are macroscopic changes that occur in a small portion of the brain and are less widespread than the abnormalities apparent by the above-mentioned techniques. These latter changes are best characterized by the term "metabolic dysfunction." Metabolic dysfunction is characterized by abnormal mitochondrial function, increased glucose metabolism and alteration of ionic homeostasis. This metabolic dysfunction is also heterogeneous and has a temporal behavior that changes over time, and may lead to alternative fuels being used in addition to glucose. While this burning of additional fuels is not apparent on either gross inspection or computerized tomography, methods such as MRS, microdialysis and PET

enable a clinical diagnosis of dysfunction. In this context, monitoring this abnormal metabolism throughout the acute post injury period may be prudent in order to provide an appropriate supply of fuel.

Microdialysis has provided an important monitor of dysfunctional metabolism in the acute setting after TBI. Microdialysis has also been able to detect the occurrence of secondary insults, such as brain ischemia and seizures, and provides a clear-cut pattern of the collapse of brain function during terminal herniation. This pattern involves collapse of brain circulation, evidenced by reduction of extracellular glucose to below detectable limits and an increase in the lactate/pyruvate ratio. Some researchers have suggested that microdialysis can serve as a prognostic tool since this pattern marks complete loss of brain function in the region of the microdialysis probe. In addition, patients with worse outcome tend to have higher glutamate and lactate values and lower glucose values in comparison to those with a good outcome (1, 9).

As an in vivo monitor, microdialysis provides on-line assessment of the utilization of glucose and lactate. In the current study, regional heterogeneity of glucose and lactate levels depends on the area sampled. Moreover, the glucose values are <0.2 mmol in regions of brain that exhibit hyperglycolysis, while lactate is increased in selected regions that display hyperglycolysis. The presence of elevated whole tissue lactate is confirmed on the H-MRS. Given the variability in brain metabolism, as confirmed by both FDG-PET and H-MRS, selection of the proper site for microdialysis monitoring is crucial for clinical management. On-line microdialysis monitoring provides a means to track important changes in brain metabolism, but regional heterogeneity must be kept in mind. Within these restrictions, microdialysis is a powerful technique.

H-MRS provides important insight into the regional heterogeneity of brain metabolism and neurochemical levels. Across a wide spectrum of traumatic brain injury, H-MRS has demonstrated significant reductions in NAA or NAA/Cr and elevations in Cho/Cr (6, 8, 15). Reference normal values of the selected analytes are as follows: NAA/Cr>4, NAA/Cho>3, and Cho/Cr>1.5 (17). Reduction in NAA is thought to reflect impairment of mitochondrial function and the ability to make

ATP (16). These changes occur in NAWM but also in pericontusional tissue. To date, there have been few studies defining the regional heterogeneity of these changes, in part because early studies on critically ill patients are difficult to do. The pericontusional region demonstrates the most profound reduction in NAA and increase in lactate while normal appearing white matter displays more normal values. Combining information from H-MRS with the microdialysis data, areas of reduced NAA/Cr demonstrate microdialysis markers of metabolic dysfunction. In addition, in the cases reported here the two H-MRS voxels adjacent to the microdialysis catheters show regional heterogeneity of the lactate values that qualitatively match the relative differences in microdialysis lactate levels. Thus, one may foresee the opportunity of using H-MRS and microdialysis in combination to monitor brain metabolism in a regional and temporal fashion.

This paper demonstrates the concept of using PET, microdialysis and MRS in an integrated way to study the heterogeneity of brain metabolism in both a spatial and temporal fashion. In addition, microdialysis can be used to validate tissue concentrations of important neurochemicals. This validation can be used to calibrate the H-MRS. Once this validation has been done, non-invasive testing such as MRS may be able to provide robust repeated measures of metabolic pathophysiology across the entire spectrum of brain trauma, including mild brain injury.

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