INVESTIGATION OF BRAIN METABOLITES AND CORTICAL GLUCOSE METABOLISM IN HUMAN PARTIAL EPILEPSY

Doctor of philosophy (PhD) dissertation

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INTRODUCTION AND STUDY BACKGROUND

Imaging plays an important role in the evaluation of patients with epilepsy and seizure disorders that have a cortical origin. Structural and functional studies including magnetic resonance imaging (MRI), proton magnetic resonance spectroscopy (^{1}H MRS), and 2-deoxy-2[F-18]fluoro-D-glucose positron emission tomography (FDG PET) are used to identify etiology and epileptogenic zone, as well as to confirm the ictal focus based on EEG recordings.

Brain metabolites, neurotransmitters and glucose metabolism in epilepsy

N-acetyl aspartate (NAA), creatine/phosphocreatine (Cr), cholin compounds (Cho) and glutamate/glutamine/γ-aminobutyric acid complex (Glx) detected by ^{1}H MRS are the principal signals of interest in epilepsy studies. NAA is the second most abundant amino acid in the human central nervous system (1), and it appears to exhibit neurotransmitter activity acting on glutamate receptors (2). NAA is localized in mitochondrium fractions and in cytoplasm of the neuron, and primarily formed in neurons from acetyl-CoA and aspartate (1). Cr and Cho are found both in neurons and glial cells, but they are present at much higher concentrations in oligodendrocytes and astrocytes than in neurons (3). Creatine is converted to phosphocreatine through the enzyme creatine kinase (3). Phosphocreatine is a high-energy phosphate, which is critical for maintaining cellular energy dependent systems (3). The Cho resonance contains contributions from a number of mobile choline compounds (3). These membrane-bound compounds are generally not MR-visible; however, in disease processes which result in membrane breakdown, the formerly bound cholin is released into free cholin pool and becomes MR-visible (3). Reduction of NAA signal and decreased NAA/(Cho+Cr) ratios have been found both ipsi and contralateral to the focus, with the ipsilateral side being more affected in patients with focal epilepsy (4-8).

Glutamate is the main excitatory neurotransmitter in the human brain and is believed to play an important role in the initiation, spread, and maintenance of epileptic activity (9). Glutamate receptors are located on glial and neuronal cells (10,11). Increases in the density of NMDA (N-methyl-D-aspartate), AMPA (α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid), and kainate receptors (12-14), and increased number of glutamate receptor subunits have been described in epilepsy (15,16). The functions of glutamate metabotropic and NMDA receptors are modified in epilepsy (17-20), and alterations in glutamate transporters also potentially can contribute to epileptogenesis (21-23). The role of glutamate in the mechanism of seizure is supported by antiepileptogenic pharmacological compounds which can decrease glutamate release acting on presynaptic terminals (24,25), while others, used in human practice reduce the extracellular glutamate concentration by sodium channel inactivation (26). Furthermore, antagonists of NMDA and AMPA receptors are anticonvulsants in animal models of epilepsy (27,28). ^{1}H MRS detects mainly the intracellular Glx pool (containing predominantly glutamate and glutamine and γ-aminobutyric acid [GABA] in lesser concentration), and these are present in both neuronal and in glial cells (3).

2-deoxy-2[F-18]fluoro-D-glucose positron emission tomography (FDG PET) is used to demonstrate the regional cerebral glucose metabolism (29) and it is often applied for the localization of epileptogenic brain regions (29,30). Regional hypometabolism identifies the epileptogenic lobe in about 80-90 % of children with refractory epilepsy who exhibit focal FDG PET abnormalities (31). In contrast, children with recent-onset epilepsy appear to have less frequent and less profound metabolic abnormalities than those with chronic epilepsy (32).

Relation between N-acetyl compounds (NA) and glutamate/glutamine metabolism

Similar to NAA, the peptide neurotransmitter N-acetyl aspartyl glutamate (NAAG), a derivative of NAA, is also localized in neurons (33) and synthesized from NAA and glutamate (34). The recently identified cellular separation of the two anabolic and two catabolic enzymes in the NAA and NAAG cycles points to a three-cell compartmentalization involving neurons (NAA and NAAG synthases), astrocytes (NAAG peptidase), and oligodendrocytes (aspartoacyclase) (35). NAAG, released by neurons, is cleaved at the cell surface of astrocytes into NAA and glutamate. NAA is hydrolyzed in oligodendrocytes, and the end products may serve message to neurons (35). Glutamate is taken up by astrocytes, and it is recycled to neurons via the glutamate-glutamine conversion (36).

NAAG may have two major roles following the synaptic release: activation of type 3 metabotropic glutamate receptors (37), and, based on its rapid turnover, delivery and production of glutamate (34). NAA also shows neurotransmitter activity (2); however, the relatively slow rate of NAA turnover suggests that its major role is as substrate for the formation of NAAG (34). In pathological states, alterations in the levels of NAAG, and in the activity of NAAG peptidase have been found decreasing or increasing the availability of NAA and glutamate in brain synapses (38-40). Both NAA and NAAG concentrations can be determined by ^{1}H magnetic resonance spectroscopy (^{1}H MRS) in vivo, since the resonance of NA at 2.02 pars per million (ppm) chemical shift value contains overlapping resonances including NAA, as well as NAAG in smaller proportion (3,41).

Coupling between glutamate and glucose metabolism

A recently articulated hypothesis suggests that the majority of the signal derived from 2-deoxy-2[F-18]fluoro-glucose (FDG) uptake measured with PET is due to glutamate stimulation of glucose uptake by astrocytes (36,42). The hypothesis regarding glutamate and glucose

coupling is based upon the observation that glutamate stimulated 2-deoxyglucose uptake and phosphorylation by astrocytes in primary culture (36,42). Glutamate uptake into the astrocytes by a glutamate transporter resulted in a concomitant stimulation of glucose uptake via a mechanism involving activation of the Na+/K+ ATPase, followed by an increase in lactate efflux from the astrocytes (43). Thus, Pellerin and Magistretti (43) have proposed that this mechanism accounts for the coupling between neuronal activity and energy metabolism. Further data to support possibly this theory are derived from [C-13]MRS studies in which cortical rates of oxidative glucose metabolism and glutamate neurotransmitter cycling were measured in rats under different degrees of anesthesia (44). An approximate 1:1 stoichiometry was reported between glutamate cycling and glucose metabolism, with glutamatergic synaptic activity accounting for over 80% of total glucose oxidation under conditions of mild anesthesia (44). All of the data supporting this hypothesis, however, were derived either from cultured astrocytes or anesthetized rodents, and therefore, the applicability of these findings to humans remains to be established.

STUDY GOALS

The goals of this study were: 1., to detect the altered signal intensity of brain metabolites in the epileptogenic region in the unstimulated interictal and stimulated ictal/periictal state in human epilepsy patients by ^{1}H MRS, 2., to determine the brain glucose utilization in the same cortical regions, 3., to investigate the relationship between NA and glutamate/glutamine metabolism based on the associations between NAAG and glutamate neurotransmission, 4., to test the hypothesis of coupling between glutamate and glucose metabolism in human epileptic

and non-epileptic cortex by comparing regional values of glucose metabolism from FDG PET studies with ^{1}H MRS measurements of Glx tissue concentration.

PATIENTS AND METHODS

Subjects. Eleven patients (five females and six males, mean age 7.5 years, age range 0.3-20 years) with medically intractable partial epilepsy were included in the study. Clinical data for these subjects are presented in Table 1. As part of the presurgical evaluation, all patients underwent MRI, quantitative single voxel ^{1}H MRS, FDG PET and prolonged video-EEG recordings with scalp and sphenoidal electrodes. Intraoperative electrocorticography was performed in two patients, and three patients underwent chronic intracranial EEG monitoring. Ictal EEG recordings were obtained in all patients. Patients were selected for the study for whom both scans were obtained for the same ictal state (i.e. either both scans were interictal (n=7) or both scans were ictal/periictal (n=4)) and for whom the antiepileptic treatment was the same during both scans. Antiepileptic treatment at the time of the FDG PET and ^{1}H MRS examinations included mono- or polytherapy with carbamazepine (n=3), clonazepam (n=2), felbamate (n=1), gabapentin (n=2), lamotrigine (n=2), phenobarbital (n=1), phenytoin (n=3), valproate (n=7), and vigabatrin (n=2). Studies were performed in accordance with the regulations of the Human Investigation Committee at Wayne State University (Detroit, USA).

PET scanning protocol. Patients were fasted for four hours prior to the PET studies. Scalp EEG electrodes were placed according to the International 10-20 system, and EEG was monitored throughout the tracer uptake period. A venous line was established for injection of FDG (0.143 mCi/kg) produced using a Siemens RDS-11 cyclotron (Knoxville, Tennessee, USA). External stimuli were minimized by dimming the lights and discouraging interaction, so

those studies reflected the resting awake state during the uptake period (0-30 minutes post injection). Sedation with intravenous pentobarbital or midazolam was used if necessary only after the tracer uptake period.

FDG PET studies were performed using a CTI/Siemens EXACT/HR whole body positron tomograph (Knoxville, Tennessee, USA). This scanner has a 15 cm field of view and generates 47 image planes with a slice thickness of 3.125 mm. The reconstructed image in-plane resolution obtained is 6.5 $\pm$ 0.35 mm at full-width-at-half-maximum (FWHM) and 6.0 $\pm$ 0.49 mm in the axial direction for the FDG PET (reconstruction parameters: Shepp-Logan filter with 1.1 cycles/cm cutoff frequency and Hanning filter with 0.20 cycles/pixel cutoff frequency). Calculated attenuation correction was performed as previously described (45).

MRI/MRS protocol. MRI and MRS exams were performed on a GE 1.5 Tesla Signa 5.7 unit (GE Medical Systems, Milwaukee, Wisconsin, USA). Multiplanar MRI sequences were obtained in all cases including a 124 slice (1.5mm) T1 weighted spoiled gradient echo (SPGR), fluid-attenuated inversion-recovery (FLAIR) and a 21 plane axial T2 weighted sequences. Sedation with intravenous pentobarbital or midazolam was used if necessary.

During ^{1}H MRS examination a Stimulated Echo Acquisition Mode (STEAM) pulse sequence (46) was used to acquire spectra using the following acquisition parameters and also included unsuppressed water reference scans for neurochemical quantitation: an echo time of 30 msec, a modulation time of 13.7 msec, a repetition time of 2 sec, 8 step phase cycle, 2048 points, a spectral width of 2500 Hz, and 128 averages for a total acquisition time of approximately 5 minutes. In vivo spectra were acquired from approximately 8cc volumes of interest (VOIs) in the region of the seizure focus and symmetrically on the contralateral side

such that they contained almost entirely gray matter and did not contain structural lesions, if present.

MRI/PET coregistration. Coregistration of FDG PET and MRI image volumes was performed as described previously, using a multi-purpose three-dimensional registration technique (MPItool) developed by the Max-Planck-Institute in Cologne, Germany (47,48). The PET image volume was coregistered with the axial MRI image volume using MPItool and a new image volume was created with 21 image planes corresponding to the original MRI image planes. Brain regions of interest (ROIs) for the position of the MRS voxels were registered on the axial T2 MRI images and then transferred to the coregistered FDG PET images.

PET image analysis. Regional values for tracer concentration were obtained by taking the average value for all planes in which the voxel was located. Regional values were then normalized to the concentration for the normal hemisphere (contralateral to the seizure focus), yielding a ratio of relative regional cerebral glucose utilization (rCGU). For the assessment of asymmetries in glucose metabolism, we used an asymmetry index (AI):

$$AI\ (\%) = (A_C - A_I)/[(A_C + A_I)/2] \times 100\ (\%)$$

where A_I and A_C are the radioactivity concentrations (μCi/ml) for the defined brain regions on the side of the seizure focus and contralateral to the focus, respectively.

Quantitative MRS analysis. Compounds, which were identified in short echo ^{1}H MRS human brain studies included NA, Glx, Cr, Cho, and myo-inositol (mI); however, the latter was not evaluated in this study. The area under each of the resonances is proportional to the concentration of the specific neurochemical compound. Individual peak areas were fit using time domain analysis software (49,50), and the concentrations of each compound are reported in arbitrary quantitative units as a ratio to brain water concentration ($x10^4$/water). This water

referencing method has been used in the field for over a decade and has been validated by a number of research groups (51-55). The analysis software is public domain (http://carbon.uab.es/mruiwww) and eliminates much of the subjectivity previously involved in determining spectral peak areas using older methods. The software performs an automated fit of the unsuppressed water peak to determine its peak area and also uses the phase of the water peak to apply an automated zero order phase correction to the metabolite data. Following this, the user enters a priori information regarding the neurochemical data in order to give the software starting values for its fitting process. The a priori information given includes the expected chemical shifts for each of the major chemical compounds appearing in the typical proton brain spectrum as well as a starting linewidth determined by the corresponding water linewidth. The chemical shift values are 2.02 ppm for NA, 2.3 for the Glx complex, 3.03 ppm for Cr, 3.22 for Cho, and 3.56 for mI based on literature values (56-59).

Statistical analysis. Statistical analysis was performed using StatView statistical package (BrainPower, Inc., Calabasas, California, USA). A Pearson's correlation was used to assess the correlation between the absolute values for NA and Glx values, as well as for Glx and relative rCGU values. The statistical significance of the correlations was calculated by F-test. $P < 0.05$ was considered to be significant.

RESULTS

Tissue concentrations of brain metabolites

Quantitative values of brain metabolites are given in Table 2. Decreased NA concentration on the side of the epileptic focus relative to the contralateral side was found in all

seven patients with interictal studies (Table 2, Figure 1A). In four patients with ictal/periictal studies, there were higher NA concentrations on the side of the EEG focus (Table 2, Figure 1B).

Similarly, decreased Glx concentration on the side of the epileptic focus relative to the contralateral side was found in all cases with interictal studies (Table 2, Fig. 1A). In patients with ictal/periictal studies, there were higher Glx concentrations on the side of the EEG focus (Table 2, Fig. 1B).

The NA and Glx quantitative values showed correct focus (as determined by intracranial and/or scalp EEG) lateralization in each case, while the NA/Cho, and the NA/Cr, metabolite ratios only in eight patients. The lateralization value of these ratios was correct in all cases when the metabolites were registered from brain regions with at least 10% FDG PET asymmetry (Table 2).

Regional brain glucose utilization

A summary of the qualitative (visual) assessment of glucose metabolism abnormalities is presented in Table 1. Various portions of the cortex and subcortical structures appeared normal; however, other parts of the brain showed abnormal glucose metabolism. The PET images revealed decreased regional cortical glucose metabolism on the side of seizure focus in all patients with interictal study, while PET images obtained during ictal/periictal state in showed increased regional glucose metabolism corresponding to the side of EEG focus (Table 1).

Quantitative values of rCGU in the epileptic focus and contralateral homotopic regions are given in Table 2. Analysis of rCGU for the region of the seizure focus showed a broad range of values, varying from a decrease of 23.8% to an increase of 16.9% compared to the contralateral homotopic normal region (Table 2). Decreased glucose metabolism was found in the seizure focus in all patients examined in the interictal state (Table 2: Patients 1-7, Figure

2A), while increased metabolism was observed in patients who had ictal studies (Table 2: Patients 8-11, Figure 2B). The rCGU values showed correct focus lateralization in all examined patients including both the ictal/periictal and interictal studies.

Relation between NA and Glx concentrations

A significant correlation was found in the comparison of tissue concentration of NA with concentration of glutamate/glutamine/γ-aminobutyric acid using ROIs in the epileptic cortex (r=0.60, p=0.048) (Figure 3A), while using contralateral homotopic ROIs, there was a tendency for statistical significant correlation (r=0.58, p=0.061) (Figure 3B).

Relation between rCGU values and Glx concentrations

Significant correlations were found in the comparison of glucose metabolism with tissue concentration of glutamate/glutamine/γ-aminobutyric acid using ROIs in the epileptic cortex (r=0.67, p=0.021), using contralateral homotopic ROIs (r=0.60, p=0.047), and using the combined ROIs from focus and non-focus regions (r=0.64, p=0.0009), (Figure 4).

DISCUSSION

In this study, we investigated brain metabolite concentrations of NA, Cr, Cho, Glx and cortical glucose metabolism in humans under normal and pathological conditions by ^{1}H MRS and FDG PET in symmetrical brain regions.

^{1}H MRS measurements in focal epilepsy

We found decreased NA concentrations in the epileptogenic brain regions relative to the contralateral side interictally, while the ictal/periictal studies showed higher NA concentrations in the same locations. The interictal results are consistent with the findings of previous MRS studies performed in patients with temporal and extratemporal lobe epilepsy (4-8). In

pathological states, decreases in the levels of NAA, NAAG, and in the activity of NAAG peptidase have been found correlating with neuronal loss (38). Normalization of decreased NAA after epilepsy surgery has been shown including both the ipsi and contralateral side (60). Thus, the reversible decrease of NAA concentration may represent decreased production due to neuronal and/or mitochondrial dysfunction, or degradation of NAA following neuronal membrane disruption (61).

In contrast, larger diversity has been shown in NAA levels by the ictal and postictal MRS studies, probably due to the differences in timing of scanning and acquisition after the seizure onset. In human studies, the values of NAA/Chol and NAA/Cr ratios were decreased in the ipsilateral temporal lobe (62,63); however, the majority of observations were made in the postictal period. In animal models, increased NA/Cr ratios were found in ictal state (64,65), while significant NAA changes were not observed postictally (66). The increased NA/Cr ratios have been considered to be a reflection of NAA synthesis increases, since negligible changes in brain Cr levels has been shown under different pathologic conditions (64).

Our data showing decreased Glx concentration interictally and increased concentration with seizure activity are consistent with previous studies. Lower Glx concentration has been shown ipsilateral to the seizure onset in patients with temporal lobe epilepsy and hippocampal sclerosis as compared to normal controls (67). Enhanced glutamate release, contributing to the initiation of seizure activity, has been reported in microdialysis studies during seizures in patients with partial epilepsy (68-70), as well as in some animal models (71,72). Increased glutamate/glutamine level was also measured with MRS after status epilepticus in one patient with focal epilepsy (62). These data suggest that Glx concentration is lower in epileptogenic brain regions than in normal tissue, but may increase with ictal activity.

The mechanism for a rapid increase in total tissue Glx during seizure activity, however, is unclear. The increase may be the result of increased flux through the glutamate/glutamine synthesis cycle. Another possible mechanism, which might contribute to a rapid increase in total tissue glutamate could be the release of glutamate through the cleavage of n-acetyl-aspartylglutamate (NAAG) (33). NAAG is released by neuronal depolarization and is converted to N-acetyl-aspartate (NAA) and glutamate by glutamate carboxypeptidase II (33), an enzyme present on the extracellular surface of glia and neurons (73). Alterations in NAAG and the carboxypeptidase activity have been reported in several animal models of epilepsy. In genetically epilepsy-prone rats, the activity of this membrane bound enzyme (74) is increased in several brain regions, which increases availability of NAA and glutamate in certain synapses of the brain (34). Kindling-induced increased NAAG level was observed in the entorhinal cortex (39,75). Furthermore, the rapid turnover of NAAG shows that the conversion of NAA to NAAG can be an important modulator of synaptic activity (40).

FDG PET measurements in focal epilepsy

The FDG PET findings presented in this study are consistent with the results of previous studies showing differences in regional glucose metabolism during interictal period and ictal epileptic status (29-32). The characteristic of an epileptogenic focus, studied interictally in lesional and nonlesional neocortical epilepsy, is an area surrounded by large areas of reduced glucose metabolism that is usually larger than the pathological abnormality (76,77). The most likely reason for the large region of reduced metabolism is inhibition or deafferentation of neurons around an epileptogenic focus (78). Partial seizures are associated with an increase in regional cerebral glucose metabolism in the region of the epileptogenic focus (79). Hypermetabolic areas have also been found in children with partial seizures, who were not

having overt seizures and in patients with cryptogenic temporal lobe epilepsy, who had never recieved antiepileptic drugs. (80). The biochemical basis of interictal and ictal hypermetabolism is probably related to increased energy consumption by an active epileptogenic focus (81).

Lateralization of seizure focus

^{1}H spectroscopic imaging of brain metabolites and FDG PET have been proven to be a sensitive indicator for the lateralization of seizure foci in focal epilepsies; however, previous studies showed different concordance between the distribution of ^{1}H MRS, FDG PET and EEG abnormalities (7,82,83). The sensitivity of ^{1}H MRS in lateralization of unilateral temporal and extratemporal lobe epilepsy varied between 55-88% showing bilateral abnormalities in less than 50% of the patients (5-8,82,83). These results were based on calculations of NAA/Cr, NAA/Cho and NAA/(Cr+Cho) metabolite ratios (5-8,82,83). Interictal FDG PET studies in patients with longstanding epilepsy predicted the side of the focus in almost all cases (31,84), though patients with recent-onset epilepsy appeared to have less intense metabolic abnormalities (30,32,78). In this study, ^{1}H MRS and FDG PET correctly lateralized the EEG focus in all patients using quantitative values of NA, Glx and rCGU, while on the basis of the NA/Cr and NA/Cho metabolite ratios just in eight children. We could achieve lateralization of the epileptogenic focus by metabolite ratios more correctly in those patients having had voxels localized to areas with more intense abnormalities in cortical glucose metabolism. In interictal studies, the decreased metabolite ratios can be due to decreases of NA concentrations and/or increases of Cr and Cho concentrations (7). Intensive metabolic abnormalities are associated with profound neuronal dysfunction causing changes in the signal intensity of NAA (82,83). The concentrations of Cr and Cho appear to be much higher in oligodendrocytes and astrocytes than in neurons (3), thus the increased signal from these compounds may reflect gliosis or consistent with reactive

astrocytosis (7,78). Conversely, there are several interictal studies with no significant changes in Cr and Cho levels (4,64). According to these observations, it is very likely that in those cases when gliosis or reactive astrocytosis are not present in epileptogenic brain tissue, the seizure focus lateralization is more precise by quantitative values than metabolite ratios.

Relation between NA and Glx tissue concentrations

Because of the method applied in this study did not allow a separation of NAA and NAAG peaks, as well as glutamate and glutamine peaks, the discussion on mechanism underlying the correlation between NA and Glx concentrations in epileptic tissue must be speculative. In addition, ^{1}H MRS detects mainly the entire NAA/NAAG and Glx tissue pools giving further methodological limitation to this study. NAA and glutamate could be derived from many possible sources including synaptic release of NAAG. NAAG have been linked to seizure disorder by kindling-induced increases of NAAG concentrations in entorhinal cortex (39,75). These increases proved to be persistent for at least one week (75). In conditions associated with increased excitability, the activity of NAAG peptidase can be elevated increasing the availability of NAA and glutamate in certain synapses of the brain (40) leading to an excess of NAA uptake to oligodendrocytes and glutamate uptake into astrocytes. Further consequences of these processes are NAA hydrolysis and glutamine synthesis (35,36). Thus, it is likely that change in balance of synthesis/release/catabolism of NAAG may play an important role in epileptic activity. In addition, conditions that increase the level of acetyl-CoA may significantly increase the synthesis of NAA. Increases in NAA levels may associate with increases in glutamate levels, since it appears that most of the NAA-derived [^{15}N]aspartate undergoes transamination resulting in the formation of [^{15}N]glutamate (85).

Relation between glucose metabolism and glutamate/glutamine concentrations

By combining FDG PET with ^{1}H MRS, it is possible to study the relationship between cortical glucose metabolism and glutamate/glutamine concentration in humans under normal and pathological conditions. Using this approach, we have found a significant positive linear correlation between cortical rCGU and the glutamate/glutamine concentration, both for the epileptic focus and for the contralateral homotopic cortex. In epileptic focus ROIs, interictal glucose hypometabolism was associated with decreased Glx concentration, while ictal/periictal increased glucose metabolism was related to increased Glx concentration. This finding is consistent with the hypothesis suggesting a relationship between glutamate cycling and glucose metabolism (43). However, several methodological limitations of our study should be addressed. First, although both FDG PET and ^{1}H MRS studies for a given patient were obtained in the same state (ictal or interictal), these were not obtained simultaneously. We have attemped to match the conditions between the two series, but even then the EEGs between the two scans almost certainly will be different. Second, the Glx peak in the ^{1}H MRS signal detects the entire tissue glutamate/glutamine pool, of which the released glutamate is only a small component (44).

SUMMARY

In conclusion, both ^{1}H MRS and FDG PET proved to be a useful diagnostic tool in the evaluation of partial epilepsies. The cortical seizure focus can be characterized by lower NA and Glx concentrations, in addition to decreased glucose metabolism interictally, and by higher metabolite levels and increased glucose utilization in ictal phase. The NA and Glx quantitative values of ^{1}H MRS studies and the rCGU values of FDG PET studies showed higher sensitivity

in focus lateralization than the NA/Cr and NA/Cho metabolite ratios. Furthermore, these results demonstrate a significant relationship between tissue glutamate/glutamine and NAA/NAAG concentrations in the epileptic cortex. Activation of NAAG catabolic pathway may explain the relation between NAA and glutamate/glutamine tissue concentrations. Finally, our data support the coupling of glucose metabolism to glutamate metabolism in the cerebral cortex, and extend previous findings to humans under normal and pathological conditions.

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PUBLICATIONS

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6. **Pfund Z**, Szapáry L, Jászberényi O, Nagy F, Czopf J. Headache in intracranial tumors. Cephalalgia 1999;19:787-790. Impact factor (1999): 2.75

7. **Pfund Z**, Chugani DC, Juhász C, Muzik O, Chugani HT, Wilds IB, Seraji-Bozorgzad N, Moore GJ. Evidence for coupling between glucose metabolism and glutamate cycling using FDG PET and ^{1}H magnetic resonance spectroscopy in patients with epilepsy. J Cereb Blood Flow Metab 2000;20:871-878. Impact factor (2000): 5.92

8. **Pfund Z**, Chugani HT, Juhász C, Muzik O, Behen ME, Chugani DC, Nigro MA, Trock GL, Squires LA. Lissencephaly: fetal pattern of glucose metabolism on positron emission tomography? Neurology 2000;55:1683-1688. Impact factor (2000): 4.78

9. Lee JS, Asano E, Muzik O, Chugani DC, Juhász C, **Pfund Z**, Philip S, Behen M, Chugani HT. Sturge-Weber syndrome: correlation between clinical course and FDG PET findings. Neurology 2001;57:189-195. Impact factor (2001): 5.21

10. Trauninger A, **Pfund Z**, Kõszegi T, Czopf J. Oral magnesium load test in patients with migraine. Headache 2002;42:114-119. Impact factor (2001): 2.80

11. **Pfund Z**, Chugani DC, Muzik O, Juhász C, Behen ME, Lee J, Chakraborty P, Mangner T, Chugani HT. α[^{11}C]methyl-L-tryptophan PET in patients with alternating hemiplegia of childhood. J Child Neurol 2002;4:253-260. Impact factor (2001): 1.39 $\Sigma_{\text{impact factors}}$: 22.85

PRESENTATIONS

Oral presentations:

1. Uremic polyneuropathy: clinical and electrophysiological analysis. 35th Congress of the Hungarian Society of EEG and Clinical Neurophysiology, October 8-10, 1992, Gyõr, Hungary

2. Multiple cerebral infarction with cardiac origin. 1th Hungarian Congress of Stroke, November 26-28, 1992, Budapest, Hungary

3. Migraine, depression, anxiety. 9th Congress of the Hungarian Young Neurologists, September 24-25, 1993, Gyõr, Hungary

4. Uremic polyneuropathy: clinical and electrophysiological analysis. The 16th Joint Annual Meeting of Societies for the EEG and Clinical Neurophysiology in Central and Eastern Europe, June 3-5, 1993, Miedzyzdroje, Poland

5. Tension type headache with organic origin. 1th Congress of the Hungarian Headache Society, May 5-6, 1994, Szentendre, Hungary

6. Migraine with white matter lesions. 2nd Congress of the Hungarian Headache Society, May 19-20, 1995, Szentendre, Hungary

7. Headaches with brain tumors. 3rd Congress of the Hungarian Headache Society, May 10-11, 1996, Balatonkenese, Hungary

8. The role of neurologist in diagnosis of autoimmun diseases. Regional Immunological Meeting, October 25-26, 1996, Mosdós, Hungary

9. Temporal inhibitory reflex in headache patients. 4th Congress of the Hungarian Headache Society, May 16-17, 1997, Balatonkenese, Hungary

10. Mitochondrial myopathies. 38th Congress of the Hungarian Society of EEG and Clinical Neurophysiology, March 23-26, 1998, Kecskemét, Hungary

11. Headache and sinus thrombosis. 5th Congress of the Hungarian Headache Society, May 15-16, 1998, Balatonalmádi, Hungary

12. $\alpha[^{11}C]$methyl-L-tryptophan PET in patients with alternating hemiplegia of childhood. 9th Congress of the Hungarian Headache Society, May 3-4, 2002, Balatonalmádi, Hungary

Poster presentations:

1. Investigations of peripheral motor reinnervation after surgical lesion of plexus ischiadicus in rabbits. 36th Congress of the Hungarian Society of EEG and Clinical Neurophysiology, October 14-16, 1993, Debrecen, Hungary

2. Investigations of peripheral motor reinnervation after surgical lesion of plexus ischiadicus in rabbits. 7th European Congress of Clinical Neurophysiology, July 3-7, 1994, Budapest, Hungary

3. Morphological and electrophysiological parameters of ALS patients. 32nd National Congress of the Hungarian Society of Neurologists and Psychiatrists and Joint Meeting of British and Hungarian Neurologists, March 7-11, 1995, Budapest, Hungary

4. Exmination of segmental dermatomal evoked potentials in children after traumatic brachial plexus lesion during birth. 37th Congress of the Hungarian Society of EEG and Clinical Neurophysiology, May 23-25, 1996, Gyula, Hungary

5. Headache in intracranial tumors. 8th Congress of the International Headache Society, June 10-14, 1997, Amsterdam, Netherland

6. Inhibitory reflexes in headaches. 4th European Headache Federation Congress, June 12-16, 1998, Corfu, Greece

7. Examination of peripheral motor reinnervation in rabbit tube spaces. IX International Congress on Neuromuscular Diseases, August 30-September 4, 1998, Adelaide, Australia

8. Evidence for coupling between glucose metabolism and glutamate cycling using FDG PET and ^{1}H MRS in epilepsy patients. Annual Meeting of the American Epilepsy Society, December 1-6, Los Angeles, USA

9. Abnormalities of $GABA_A$ receptors measured with [^{11}C]flumazenil PET in autistic children. November 10-15, 2001, 31st Annual Meeting of Society for Neuroscience, San Diego, USA

10. Sturge-Weber syndrome: quantitative MRI and FDG PET correlations. Annual Meeting of the American Epilepsy Society, November 30-December 5, 2001, Philadelphia, USA