

Reduced concentrations of GABA and NAA in the thalamus of patients with juvenile myoclonus epilepsy

Ulrich Pilatus¹, Christian Lücknerath¹, Stefanie Pellikan¹, Dmitri Vronski¹, Susanne Knake², Matthias Kieslich³, and Elke Hattingen¹

¹Institute of Neuroradiology, Goethe-University Frankfurt, Frankfurt, Germany, ²Centrum of Epilepsy Hessen, Philipps-University Marburg, Marburg, Germany,

³Department of Pediatric Neurology, Goethe-University Frankfurt, Frankfurt, Germany

Introduction: Juvenile myoclonic epilepsy (JME) is characterized by awakening myoclonus, often associated with tonic-clonic seizures and absences and subtle frontal lobe pathology (1). Dysfunction of thalamocortical circuits is considered to trigger myoclonic seizures in JME (1). The thalamus amplifies and synchronizes thalamocortical rhythms which involve pyramidal cells of the motor cortex. This thalamocortical network is reciprocally connected by excitatory glutamatergic and inhibitory GABAergic projections. Congenital alterations of GABAergic neurotransmission play a key role in JME (2) and it has been shown in vivo that GABA concentrations are decreased in the occipital brain of JME-Patients (3). In addition, some antiepileptic drugs have been shown to influence cerebral GABA concentrations (4). Therefore, we evaluated changes of the neurotransmitter concentration in thalamocortical and frontal regions of JME patients with MR spectroscopy (MRS) by comparing JME patients to healthy subjects.

Materials and Methods: Thalamus, frontal lobe, and motor cortex were studied in 15 JME patients and 15 age-matched controls. All spectroscopic measurements were performed on a 3 Tesla scanner (Siemens AG, Erlangen, Germany). Single voxel spectroscopy (SVS) was used to measure 1H MRS detectable metabolite concentrations in the thalamus, the frontal lobe and the motor cortex of the dominant hemisphere. In addition, a 1H MR spectroscopic imaging (MRSI) was performed. The MRSI slice was oriented to measure brain metabolites in the grey and white matter of both hemispheres covering the thalamus and the motor cortex offering metabolite information from the respective non-dominant target regions. The main 1H MRS detectable metabolites (NAA, creatine, choline and myoinositol, glutamine and glutamate) were obtained from short TE (30 ms) PRESS spectra, while a single voxel MEGA-PRESS sequence at a TE of 70 ms was used for the detection of GABA (selective excitation at 1.9 ppm) (5). To allow gray-white matter segmentation, the protocol included a sagittal-oriented magnetization-prepared rapid gradient echo (MPRAGE) sequence. The short TE 1H MRS spectra were analyzed with the software tool LCModel (<http://s-provencher.com>) while the GABA-edited data were analyzed with jMRUI (<http://www.mrui.uab.es/mrui>). Metabolite concentrations from patients were compared to control subject using ANOVA. In addition, we divided the patients into two groups: patients with valproate treatment and patients who received other drugs but no valproate. Statistical analysis was performed with STATISTICA (version 7.1; StatSoft, Tulsa, OK, USA)

Results: Concentrations of the metabolites GABA (obtained by MEGA-PRESS for the three target regions in the dominant hemisphere) and of NAA (obtained by MRSI for right and left thalamus) are shown in Figure 1. Comparing patients (Pat) to control subjects (Prob) we found increased GABA concentrations in the frontal region ($p=0.046$) and decreased GABA in the thalamus ($p=0.033$). The NAA concentration was decreased in the dominant thalamus ($p=0.024$).

When patients were dichotomized into a group treated with valproate and a group without valproate we found significantly increased glutamine in the thalamus of valproate treated patients. There was also a consistent trend of an increase in glutamine and a decrease in myoinositol in the other regions. On the other hand, patients treated with the other drugs, showed a consistent increase in GABA and NAA in all monitored regions.

Discussion and Conclusion: We found a significant decrease of GABA and NAA concentrations in the thalamus of the dominant hemisphere in JME patients. Although treatment significantly affects metabolite concentrations, this difference is specific for JME. Since the MRSI data reveal most prominent changes for NAA concentrations in the dominant hemisphere indicating lateralization of metabolic effects. This emphasizes that regional and hemispheric differences in healthy subjects and patients, as well as influence of antiepileptic drugs, have to be taken into account for interpreting metabolite changes in JME patients.

Reduced inhibitory GABA neurotransmission in the thalamus as key region for seizure triggering may be a potential cause of JME. Further, decreased thalamic GABA transmission and neuronal damage may be mutually linked. The elevated GABA and glutamine in the frontal lobe hint to an up-regulated glutamate/GABA-glutamine system which may be part of frontal dysfunction in JME patients.

References

1. O'Muircheartaigh J, Vollmar C, Barker GJ, et al. Brain 2012;135:3635-44.
2. Cossette P, Liu L, Brisebois K, et al. Nature 2002;31:184-89.
3. Petroff OA, Hyder F, Rothman DL, Mattson RH. Neurology. 2001 Mar 27;56(6):709-15.
4. Kuzniecky R, Ho S, Pan J, et al. Neurology 2002;58:368-72.
5. Mescher M, Merkle H, Kirsch J, Garwood M, Gruetter R. NMR Biomed 1998;11:266-72.

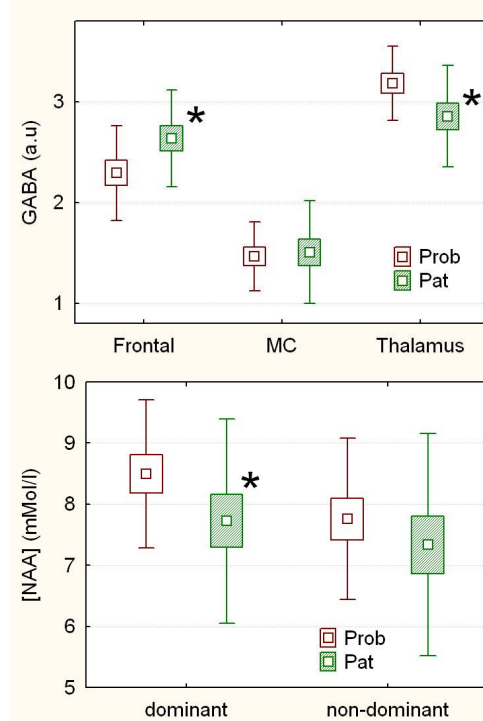


Figure 1: Concentrations of GABA and NAA comparing data from JME-patients (Pat) to control subjects (Prob) in different brain regions. Upper panel: frontal cortex, motor cortex, and thalamus of the dominant hemisphere; lower panel: dominant vs. non-dominant thalamus..