

MRS at 3 tesla in brain of schizophrenic patients: elevated glutamate in hippocampus decreases on therapy

F. Schubert¹, F. Seifert¹, K. Leopold², M. Krebs², I. Haeke², J. Gallinat², and M. Schaefer²

¹Physikalisch-Technische Bundesanstalt, Berlin, Berlin, Germany, ²Psychiatry, Charite University Medicine

Introduction

Recent findings have revitalized the glutamate hypothesis of schizophrenia [1,2]. As improved methods for the selective determination of glutamate in brain using proton MRS emerge with increasing field strength [3,4], the role of this neurotransmitter in the schizophrenic brain in vivo during therapy can be examined more profoundly. Following the glutamate hypothesis one might expect abnormal levels of glutamate in distinct gray matter regions. Recent MRS studies at 2 T [5,6] have indeed observed increased glutamate concentrations in the hippocampus of schizophrenic patients. However, examinations of therapeutic drug effects on cerebral glutamate are lacking. In an ongoing study we performed proton MRS in hippocampus and different cingulate regions of schizophrenic patients and healthy controls, focusing on quantitation of glutamate in order to test the influence of a combination therapy of neuroleptics and memantine, an uncompetitive antagonist at glutamatergic NMDA receptors used in Alzheimer therapy, on cortical glutamate. For completion, other metabolites were quantified in parallel.

Subjects and Methods

Thirty patients (age 18 to 40 years) with schizophrenia according to DSM-IV criteria were studied, of which 17 were diagnosed as acute patients and 13 as chronic patients. All patients were on neuroleptic (risperidone) therapy for at least 2 weeks (acute) and 3 months (chronic). For comparison, 30 healthy age matched volunteers were examined. All subjects gave written informed consent. MR examinations were performed on a 3T-scanner (MEDSPEC 30/100, Bruker Medical) using a Tx/Rx birdcage head coil. Following T_1 -weighted imaging of the whole brain at a resolution of $1 \times 1 \times 1.5 \text{ mm}^3$, proton spectra were acquired using PRESS optimized for glutamate detection [4] ($T_E = 80 \text{ ms}$, $T_R = 3 \text{ s}$, $n = 128$) from 3 voxels: $2 \times 3 \times 2 \text{ cm}^3$ including the left hippocampus (HC), $2.5 \times 4 \times 2 \text{ cm}^3$ including the anterior cingulate gyrus (AC), and $2 \times 2 \times 2 \text{ cm}^3$ including the posterior cingulate gyrus (PC). After the baseline examination patients of each group (acute or chronic) received additional therapy with either memantine or placebo in a double blind study design. After 6 weeks a second MR examination was performed, giving particular attention to the accurate repositioning of the spectroscopic voxel. For metabolite quantitation a time domain-frequency domain program package [4] was employed including automatic retrospective frequency drift correction, non-parametric background estimation, and uncertainty assessment using a Bayesian approach that accounts for background fit uncertainty [7]. NAA, glutamate (Glu), choline-containing compounds (tCho), creatine plus phosphocreatine (tCr), and glutamine resonances were quantified, including a basis set and prior knowledge for frequency, linewidth and phase. For quantitation an external water phantom was used; fitted amplitudes were corrected for relaxation times (determined in 3 volunteers), coil loading differences, and cerebrospinal fluid content of the voxels (obtained from segmentation using SPM2).

Results and Discussion

Uncertainties (ie CRLB + background uncertainty) for the determination of NAA, Glu, tCho and tCr amounted to 2.2 – 15.6 %. Uncertainties for glutamine were too large ($> 50 \%$) for consideration in further analysis. The only differences at baseline between patients and controls were elevated Glu (11.9 mmol/l vs 10.7 mmol/l, $p = 0.007$) and decreased NAA (11.0 mmol/l vs 11.5 mmol/l, $p = 0.02$) in the HC voxel of patients. At the time of writing, 12 patients of each group had completed the follow-up session. The figure shows the mean levels of Glu (\pm standard deviation) in the HC voxels of controls compared to all patients, and of the two patient groups at baseline and after 6 weeks of combination therapy (risperidone + memantine/placebo). Glu significantly dropped in the group of acute schizophrenics, in contrast to the chronic group, where the level remained unchanged. There were no significant differences in tCho and tCr levels in the HC voxel. None of the differences was due to different CSF contents of the voxels. There were no differences in Glu nor any other metabolite concentration between baseline and follow-up examination in the AC and HC voxels.

These results (i) confirm the recently reported Glu increase in hippocampus in schizophrenia [5]. (ii) In a region playing a key role in the pathophysiology of schizophrenia in acute patients the enhanced Glu level (initially as high as in chronic patients) tends to normalize on combined neuroleptic-memantine therapy. Unblinding of the trial will shed further light on the strength of this effect.

References

- [1] Coyle JT, Biochem Pharmacol 2004, 68:1507.
- [2] Paz RD, Eur Neuropsychopharmacol 2008, 18:773.
- [3] Hurd R, Magn Reson Med 2004, 51:435.
- [4] Schubert F, Neuroimage 2004, 21: 1762.
- [5] Tebartz van Elst, Biol Psychiatry 2005, 58:724.
- [6] Olbrich HM, World J Biol Psychiatry 2008:59.
- [7] Elster C, Magn Reson Med 2005, 53:1288.

Acknowledgement: We are grateful for the support by a grant of the Stanley Medical Research Institute (02T-247)

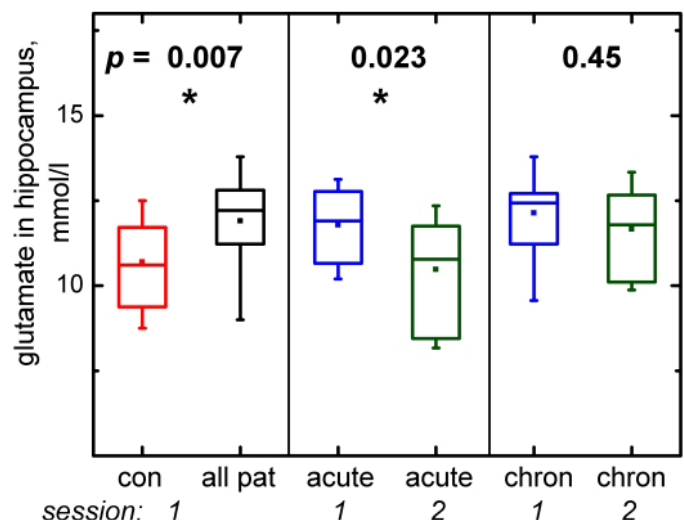


Fig.: Comparison of glutamate levels measured in the HC voxel in healthy controls (con) and schizophrenics (separated in acute and chronic patients before and after therapy).