Glutamine synthetase in epilepsy - analysis of brain and blood

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Glutamate is the major excitatory neurotransmitter of the brain. To prevent excitotoxicity, low extracellular glutamate levels are maintained by removal of glutamate from the synaptic cleft, predominantly by the glial glutamate transporter EAAT2. Glutamate is converted to glutamine by the enzyme glutamine synthetase (GS). Glutamine then diffuses to neighboring cells, including neurons and is converted to glutamate again by glutaminase, thereby closing the so-called glutamate-glutamine cycle. Neurological disorders, such as epilepsy and amyothropic lateral sclerosis (ALS), have been associated with a dysfunction of the glutamate–glutamine cycle.
In this study we examined the key enzyme glutamine synthetase in brain and blood of patients with temporal lobe epilepsy (TLE) and ALS. We analyzed the expression and activity of GS in the epileptic hippocampus and determined GS expression in leukocytes and blood platelets. In the hippocampus of patients with hippocampal sclerosis (HS) glial GS expression was found to be decreased in areas with neuronal cell loss (CA1, CA3 and CA4) and relatively preserved in CA2 and dentate gyrus. Neuronal cell loss was confirmed by Nissl staining. The reduction in GS expression was accompanied by a decrease in GS enzyme activity (* $p = 0.001$). Blood platelets and leukocytes contain GS as shown by Western blotting, and RT-PCR, sequencing and enzyme activity, respectively. Blood platelets of ALS patients expressed more GS protein than platelets of healthy volunteers.
In conclusion, the hippocampus of TLE patients with HS expressed reduced levels of GS especially in areas with neuronal degeneration. To what extent this impairment of the glutamate-glutamine cycle is a cause or a consequence of neuronal cell loss remains to be determined. Secondly, both blood platelets and leukocytes express functional GS. We found that GS expression is increased in blood platelets of ALS patients. We hypothesize that changes observed in the brain of epilepsy patients may be monitored by changes in blood cells.

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Poster session Neuroscience 2