Reduced hippocampal glutamine synthetase in temporal lobe epilepsy patients is associated with neuronal loss

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Increased levels of the excitatory neurotransmitter glutamate have been reported in the epileptogenic hippocampus of patients with temporal lobe epilepsy (TLE). This sustained increase, which may contribute to the initiation and propagation of seizure activity, indicates impaired clearance of glutamate released by neurons. Glutamate is predominantly cleared by glial cells through the excitatory amino acid transporter 2 (EAAT2) and the subsequent conversion of glutamate to glutamine by the glial enzyme glutamine synthetase (GS).
In this study we examined the hippocampal distribution of GS, EAAT2, and glial fibrillary acidic protein (GFAP) by immunohistochemistry in TLE patients with (HS group) and without severe hippocampal sclerosis (non-HS group), and in autopsy controls without neurological disorders (control group). In hippocampal homogenates we measured relative protein amounts by immunoblotting and GS enzyme activity using a colorimetric assay.
In the control and non-HS group GS immunoreactivity (IR) was predominantly found in glia in the neuropil of the subiculum, of the pyramidal cell layer of all CA fields, and in the supragranular layer of the dentate gyrus. In the HS group, GS and EAAT2 IR were markedly reduced in subfields showing neuron loss (CA1 and CA4). GFAP IR was predominantly found in these hippocampal areas with severe neuronal death and gliosis, thus showing a distribution almost complementary to that for GS and EAAT2. The reduction in GS IR observed in the HS group was confirmed by immunoblotting and paralleled by a decrease in GS enzyme activity.
Our data show that glial GS is down-regulated in the HS hippocampus of TLE patients in areas with severe neuron loss and thus implicate neuronal factors in the regulation of GS expression. This down-regulation seems to be pathology-related rather than seizure-related and may be part of the mechanism underlying impaired glutamate clearance found in the hippocampus of TLE patients with HS.

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