INDUCTION OF THE WNT INHIBITOR, DICKKOPF-1, IS ASSOCIATED WITH NEURODEGENERATION RELATED TO TEMPORAL LOBE EPILEPSY

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Hippocampal sclerosis is typically associated with mesial temporal lobe epilepsy, and is characterized by neuronal loss and reactive gliosis, most prominently in the CA1 field of the hippocampus, followed by the hilus, CA4 and CA3 fields. Although this association has been known for a long time and complicates the clinical outcome of temporal lobe epilepsy, the molecular mechanisms by which seizures cause hippocampal damage are only partially identified. Seizure-induced neuronal damage involves an excitotoxic component. Inhibition of the Wnt pathway by the secreted glycoprotein, Dickkopf-1 (Dkk-1) has been related to processes of excitotoxic and ischemic neuronal death. We now report that Dkk-1 is induced in neurons of the rat olfactory cortex and hippocampus degenerating in response to seizures produced by systemic injection of kainate (12 mg/kg, i.p.). There was a tight correlation between Dkk-1 expression and neuronal death in both regions, as shown by the different expression profiles in animals classified as "high" and "low" responders to kainate. For example, no induction of Dkk-1 was detected in the hippocampus of "low" responder rats, in which seizures did not cause neuronal loss. Induction of Dkk-1 always anticipated neuronal death and was associated with a reduction in nuclear levels of β-catenin, which reflects an ongoing inhibition of the canonical Wnt pathway. Intracerebroventricular injections of Dkk-1 antisense oligonucleotides (12 nmol/2 µl) substantially reduced kainate-induced neuronal damage, as did a pretreatment with lithium ions (1 mEq/kg, i.p.), which rescue the Wnt pathway by acting downstream of the Dkk-1 blockade. Taken collectively, these data suggest that an early inhibition of the Wnt pathway by Dkk-1 contributes to neuronal damage associated with temporal lobe epilepsy. We also examined Dkk-1 expression in the hippocampus of epileptic patients and their controls. A strong Dkk-1 immunolabeling was found in 6 bioptic samples and in one autoptic sample from patients with mesial temporal lobe epilepsy associated with hippocampal sclerosis. Dkk-1 expression was undetectable or very low in autoptic samples from non epileptic patients or in bioptic samples from patients with complex partial seizures without neuronal loss and/or reactive gliosis in the hippocampus. These data raise the attractive possibility that drugs able to rescue the canonical Wnt pathway, such as Dkk-1 antagonists or inhibitors of glycogen synthase kinase-3β, reduce the development of hippocampal sclerosis in patients with temporal lobe epilepsy.