Brain injury-induced synaptic reorganization in hilar inhibitory neurons is differentially suppressed by rapamycin

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Following traumatic brain injury (TBI), treatment with rapamycin suppresses mTOR activity and specific components of hippocampal synaptic reorganization associated with altered cortical excitability and seizure susceptibility. Re-emergence of seizures after cessation of rapamycin treatment suggests, however, an incomplete suppression of epileptogenesis. Hilar inhibitory interneurons regulate dentate granule cell (DGC) activity, and de novo synaptic input from both DGCs and CA3 pyramidal cells after TBI increases their excitability, but effects of rapamycin treatment on the injury-induced plasticity of interneurons is only partially described. Using transgenic mice in which enhanced green fluorescent protein (eGFP) is expressed in the somatostatinergic subset of hilar inhibitory interneurons, we tested the effect of daily systemic rapamycin treatment (3 mg/kg) on the excitability of hilar inhibitory interneurons after controlled cortical impact (CCI)-induced focal brain injury. Rapamycin treatment reduced, but did not normalize, the injury-induced increase in excitability of surviving eGFP+ hilar interneurons. The injury-induced increase in response to selective glutamate photostimulation of DGCs was reduced to normal levels after mTOR inhibition, but the post-injury increase in synaptic excitation arising from CA3 pyramidal cell activity was unaffected by rapamycin treatment. The incomplete suppression of synaptic reorganization in inhibitory circuits after brain injury could contribute to hippocampal hyperexcitability and the eventual reemergence of the epileptogenic process upon cessation of mTOR inhibition. Further, the cell-selective effect of mTOR inhibition on synaptic reorganization after CCI suggests possible mechanisms by which rapamycin treatment modifies epileptogenesis in some models but not others.